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EPIDEMIOLOGY, INCLUDING GENETICS

II 1

The study of genetic polymorphism in leprosy – perspectives and pitfalls

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Genetic factors provide a tempting hypothesis for explaining some apparently discordant features in the epidemiology of leprosy. In order to find evidence of a genetically determined susceptibility or resistance to leprosy, and more specifically to lepromatous leprosy, cross-sectional controlled surveys of various genetic markers have been conducted in leprosy patients. The polymorphisms investigated included nine blood groups systems, the enzyme Glucose-6-phosphate dehydrogenase, and five serum globulins. With the exception of one serum antigen (Australia antigen), which seems to be more common in patients with lepromatous leprosy, and possibly of blood group O, whose distribution in lepromatous patients is suggestive of an association with the duration of the disease, results are either negative or controversial.

Investigations of genetic markers in relation to capacity to develop Mitsuda reactivity and *in vitro* behaviour of monocytes for *M. leprae* should yield further information on the mechanism of a possibly inherited resistance of the host to lepromatous leprosy.

II 2

Epidemiological and twin studies in the investigation of leprosy resistance

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1. Two main lines of investigations in leprosy have recently been explored by geneticists. One of them is represented by the study of the association of leprosy and genetic markers, in order to look for pleiotropic effects on susceptibility to this disease. The other approach that has been applied is referred to the distribution of the early and the late lepromin reactions in families.

2. Other lines of research, however, should be explored, namely those related to the epidemiology of leprosy and to twin analysis. In spite of the several methodological pitfalls underlying most of the data found in the relevant literature, the data are used to support the hypothesis of an etiological duality of leprosy.

3. While discussing the methodological pitfalls, the author presents data on the following investigations:

3.1 Evaluation of the environmental and genetic influence on the Mitsuda reaction by the analysis of 127 twins collected in elementary schools.

3.2 Demonstration that family occurrence of leprosy is not random, by applying an *a priori* method to 961 sibships from an area of high leprosy prevalence.

3.3 Demonstration that the polar forms of leprosy have a family pattern by showing that among 111 sib-pairs belonging to different sibships, the distribution deviated significantly from that expected if the distribution were random.

3.4 Evaluation of the sex influence in leprosy contagion, by calculating the combined estimate for the relative incidence of leprosy among sexes in 1541 sibships with at least one leprosy patient.

4. As an addendum, a programme that may contribute to the discovery of new clues for further investigations on the mechanism of leprosy resistance is offered.

II 3

Field studies on the nature of reactivity to lepromin

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Field studies by the Leonard Wood Memorial and others regarding the nature, significance and possible sources of reactivity to lepromin

are reviewed. In the Philippines, as in other endemic areas, the population is extremely reactive to lepromin; infants are lepromin-negative, but reactivity increases very sharply with age and adults are almost all positive. Evidence is presented relating to the highly non-specific nature and sources of reactivity to lepromin, mostly from studies conducted in Cebu, which also show that positive Mitsuda reactions may occur even in the absence of nfection with leprosy or tuberculosis.

II 4

The epidemiology of leprosy – the Karimui trial

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This paper will present the epidemiological features of leprosy as found in an isolated, leprosy-endemic, tuberculosis-free and untreated population. The total population of Karimui has been under close observations since 1962 and all data presented are related to accurate total-population-based denominators. Over 90% of all cases of leprosy detected were confirmed histopathologically. Prevalence rates range from one village with 20% affected, to a group of villages with a population of approximately 800 in which not a single case was found, nor known to have occurred in the past: this uneven distribution can be related to patterns of bride exchange. The significance of cultural factors on the spread of the disease will be discussed.

The incidence of the disease since 1962 has remained fairly steady at 0·6% per annum. The source of infection of these new cases will be discussed in detail, using indices of exposure based on the type of leprosy to which the individual was exposed, and upon opportunities for contact within the household, the clan group and during visits to other households.

The natural history of leprosy will be discussed, particularly the phenomenon of spontaneous healing (observed in 15% of the cases). The distribution of lepromin and tuberculin reactivity in this population will be related to prevalence, incidence and the natural progress of the disease.

II 5

The frequency and distribution of acid-fast skin positivity in asymptomatic persons in Bengal villages

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General epidemiological information supports the possibility that up to two-thirds of new leprosy cases occur without known association with patients with recognised leprosy. To explore specifically the possibility of a carrier state, longitudinal studies of the natural history and transmission patterns of leprosy have been conducted in three Bengal villages near Purulia. Repeated intensive case finding surveys are supplemented by ear lobe skin biopsies on almost 80% of the eligible population. These biopsies are processed by the acid-fast bacillus concentration technique which has previously been shown on blind readings to produce the following results:

94 Lepromatous family contacts –
Positive for acid-fast bacilli about 10%.
80 Tuberculoid family contacts –
About 2%–3%.
50 Controls in non-endemic Punjab villages –
All negative .

The positive biopsies are negative to all standard cultural methods for cultivable acid-fast organisms. Other efforts are being made to identify these organisms definitively.

Results will be presented showing the relations between clinically diagnosable cases and individuals who have no recognisable evidence of disease but are positive for acid-fast bacilli on skin biopsy.

Epidemiological implications for understanding of transmission patterns will be analysed.

II 6

Unknown and non-family sources of contagion in leprosy

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The authors wish to measure the epidemiological importance of the *unknown and*

non-family sources of contagion in patients under the care of the Rovisco Pais Hospital. For this, they consulted the case histories of those 511 patients (registered from 1960 to 1967) and, for each one, noted the source of contagion and the clinical form of the disease.

The sources of contagion were classified into (1) known (family and non-family), and (2) unknown.

1. Patients who had known sources of contagion:

	Male	Female	Total
Family	99	87	186
Non-family	39	25	64
Totals:	138	112	250

2. Patients who had no known source of contagion:

Male	Female	Total
165	96	261

3. Clinical forms:

	Known sources of contagion	No known sources of contagion
Lepromatous	144	160
Tuberculoid	61	58
Undifferentiated	29	22
Dimorphous	13	17
Not yet classified	3	4
Total:	250	261

The authors comment on the following matters:

1. The epidemiological importance of the unknown sources of contagion: 51%.

2. The appreciable proportion of non-family contagions: 12·5%.

3. The approximately equal distribution of lepromatous patients with known and unknown sources of contagion.

In view of these data, the authors consider the systematic control of carriers to be as important as the diffusion of knowledge of leprosy among the doctors resident in endemic areas.

II 7

Exposure to Leprosy
An anthropological method for measuring exposure to leprosy in a leprosy endemic population at Karimui

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This paper sets out a method used to develop an exposure score for each member of a community in which all diagnosable sources of leprosy were known at a given time.

In any social context, people have different degrees of exposure to each other depending on their age, sex, marital status, and group affiliations. A Social Distance Scale was developed which allowed any person in this community to be scored relative to any other person, allowance being made for all the factors mentioned above.

If leprosy is a contact disease, then where a person lives, where he grew up, and where he visits are three significant contact situations. Therefore each person was scored for "origin", "residence" and "major visiting" pattern.

Anthropological field work was carried out to provide the data requred for every member (approximately 6,000) of the study community. This information was then coded and a computer programmed to develop and tabulate the scores. The scores represented numerically the minimum known exposure of each person to cases of each type of leprosy.

These scores were then available to test certain hypotheses put forward about leprosy and its transmission.

II 8

Epidemiology
Acid-fast organisms in the skin of the foetus and human subjects other than leprosy cases

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Nishimura has reported previously on the presence of the murine leprosy bacillus and non-cultivable acid-fast bacilli in the skin of

healthy mice which have had no contact with murine leprosy rodents, and from this it was assumed that various acid-fast organisms might be present in the human skin. The skin of human subjects other than leprosy patients is therefore being examined for the presence of acid-fast organisms.

As stated in Report I, published in "La Lepro, Vol. 34, 358 (1965)", acid-fast organisms are present in a considerably high rate and test performed with an acid-fast bacillus isolated from the skin tissue of one case gave a negative lepromin reaction in 2 cases of LL, 2 cases of TL, positive reaction in 2 healthy subjects and a negative reaction in the subject from which the organism was isolated. In another case, acid-fast bacilli were observed in the skin-tissue specimen.

In the present study, utmost care was exercised to avoid contamination by acid-fast organisms and samples of skin tissue were taken from material obtained at surgery and foetal material. The chloroform method of collection was used and if acid-fast organisms were successfully detected, the attempt was made to cultivate them. Up to the present time, acid-fast organisms have been detected from 5 out of 45 adult samples (11%) and 6 out of 34 foetal samples (18%). Cultivation has been unsuccessful in all the cases.

This finding that acid-fast organisms could be detected not only from adult material but also from foetal material is very interesting from the view-point of transplacental transmission and immuno-tolerance due to leprosy-bacillus-like organisms.

II 9

Evaluation of leprosy of the earlobe: clinical and dermatopathological study

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A comparison study of clinical impression and dermatopathological examination of earlobe skin from 100 patients in the USPHS clinic was conducted to answer these questions:

1. Is there a correlation between the clinical diagnosis and histopathological findings in the earlobe skin?

2. Does the biopsy of the earlobe provide more precise information than the classic skin scraping?

Findings

1. Patients with lepromatous leprosy correlated completely with clinical findings. Surprisingly, those patients with ENL mirrored this pattern even though the earlobe appeared normal. In those patients with inactive lepromatous leprosy the reaction was either a residual foamy histiocytic infiltrate (without acid-fast bacilli) or a non-specific chronic dermatitis.

2. Patients with dimorphous leprosy revealed different patterns: typical dimorphous, indeterminate type, non-specific granulomatous changes and non-specific chronic dermatitis.

3. Tuberculoid leprosy demonstrated only a non-specific dermatitis. One patient with dimorphous-tuberculoid leprosy showed a single beaded bacillus in the nerve of one earlobe.

4. Control specimens from patients with psoriasis or healthy individuals revealed only a non-specific dermatitis.

5. One patient with enigmatic pain and no dermatological manifestations was studied twice, each biopsy revealed indeterminate pathology with a single bacillus in the earlobe.

6. Three contacts of active leprosy patients revealed indefinite foamy histiocytic infiltrate without acid-fast bacillus.

Conclusions

1. Correlation of clinical diagnosis and histological examination findings in earlobes is best in lepromatous leprosy.

2. Except for particular patients, skin scrapings provide equivalent information as that of histopathological examination of the earlobe.

II 10

Epidemiological study of leprosy in Guanabara State, Brazil

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The authors study the endemic situation of leprosy in the State of Guanabara, as at December 31st, 1967, using data collected over

the previous five years. They make an analysis of the clinical forms and social environment of the patients, and establish an index of morbidity.

The patients were studied regarding age, sex, and economic status. Methods of case-finding were examined.

Special emphasis is laid on the analysis of 3,000 contacts, observed during a period of 18 months.

II 11

Prevalence of tuberculosis among leprosy patients

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From the review prepared in 1963 by the Director of the National Leprosy Control Programme, Government of India, it is estimated that 300 million people are living in the endemic zones and that the estimated number of people with leprosy in India is 2·5 million.

To make an assessment of the prevalence of tuberculosis among leprosy patients, information was collected only from those institutions having facilities for bacteriological diagnosis.

Analysis

Out of 89,532 leprosy patients under treatment in 66 Leprosy Control Units, there were 476 with tuberculosis – 273 among non-lepromatous and 189 among lepromatous patients. The prevalence rate works out at 0·53%.

Out of 42,532 patients in 59 in-patient institutions, there were 808 with tuberculosis – 351 among non-lepromatous and 457 among lepromatous patients. The prevalence rate works out at 1·9%. The gross prevalence rate of tuberculosis among the leprosy patients is found to be higher in the in-patient institutions than in ambulatory services, the reasons being understandable.

The gross prevalence rate of tuberculosis in India is about 1·5%, and that of leprosy is about 0·85%.

II 12

Leprosy in Italy

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In Italy, leprosy is not a serious public health problem, because it exists only sporadically or in scattered endemic foci in one region.

On 1st January, 1968, the number of reported cases was 574; nearly all of them (92%) were lepromatous, and all were under health control, either at home or in the special hospitals.

During the course of the last 15 years, 329 new patients have been reported, but that is due rather to a more efficient tracking down of the patients, who previously avoided all checks, than to a rise in the prevalence of the disease.

In fact, the habit of hiding cases of leprosy, due to the social consequence to which people suffering from this disease were exposed, continues up to the present day. This resistance has now been almost entirely overcome, due to health education and the provision of a daily subsidy to all leprosy patients as well as to the members of their families.

The hospital treatment which is advised in the case of contagious patients, is always voluntary, and the patients who are in hospital are always free to return to their homes.

The children are removed, as soon as possible, from the infected centre or suspect, but this removal is always carried out with the consent of the parents.

II 13

Cancer mortality among leprosy patients

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To test hypotheses regarding the rôle of the immune system in the pathogenesis of malignancies, the cancer mortality experience of leprosy patients was determined. Follow-up information was obtained for 848 patients whose first admission to the U.S. Public Health Service Hospital, Carville, Louisiana, occurred

between 1939 and 1963, inclusive. The expected number of cancer deaths was calculated by multiplying the person-years at risk of the leprosy patients by the age, sex, race, and calendar year specific United States mortality rates for all cancers, leukemia, and lymphoma.

There were 23 cancer deaths observed as against 19·71 expected, not a significant excess. Race, sex, age at admission, and duration of follow-up did not influence the ratio of observed to expected cancer deaths. Site distribution of the cancers was not unusual. Two cases of leukemia/lymphoma were observed as against 1·66 cases expected.

The findings of the present study do not support the hypothesis that the defects of cellular immunity observed in leprosy patients predispose to the development of malignancies. The data also do not support the hypothesis that chronic stimulation of the lymphoproliferative system predisposes that system to the development of malignancy.

II 14

Epidemiology of leprosy in Senegal

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42,000 patients with leprosy have been recorded in Senegal among a population of 2,800,000 people, representing a prevalence of 16 $^{0}/_{00}$. The lepromatous level is low, being 5%, which is the level in countries where leprosy has existed for many years.

Factors favourable to a high prevalence are:

1. *The climate.* Prevalence reaches 50 to 70 $^{0}/_{00}$ in the warm, humid south area, 30 $^{0}/_{00}$ in the savannah and 10 $^{0}/_{00}$ in the semi-desert northern area.

2. *Social aspects.* The population in the south and the savannah is sedentary, whereas in the north it is nomadic.

3. *Urban problems.* 300,000 residents in Dakar have low standards of hygiene, Of 102 patients followed at the Dermatology Clinic from 1959 to 1967, 69% had tuberculoid, 17% indeterminate, and 14% lepromatous leprosy. Family infection was found in only 5%.

In conclusion

Low standards of hygiene in the dwellings, and the climate are the main factors favouring high prevalence of leprosy. Nutritional factors are of secondary importance: family inquiries are not important in Senegal. As material resources are rather poor in Senegal, the fight against leprosy should be directed mainly against infectious cases and leprosy in children. Hence the importance of leprosy isolation villages.

II 15

Epidemiological aspects of hanseniasis in the state of São Paulo (Brazil) in the quinquennium 1962–1966

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The author analyses the main features of 8,856 patients recorded in the Leprosy Prophylaxis Services in the State of São Paulo, during the period 1962 – 1966, analysed according to clinicial appearances, age, sex, and the mode of onset.

He observes in this period a continuation of the slow diminution of the incidence of leprosy that has been proceeding since 1935. From 1924 to 1966, the proportion of patients with indeterminate leprosy increased from 18·4% to 26%. However, during the quinquennium under study the extrmes have been 29·5% in 1962 to 26% in 1966. In this period, the proportion of patients with lepromatous leprosy showed slight differences.

With reference to the age at onset, 12·74% of the patients were under 20 years, 63·39% were between 21 and 50 years, and 22·85% more than 50 years.

There was a preponderance of males, principally in the indeterminate and the lepromatous groups. In both cases, this preponderance appeared at puberty and increased with age.

The procedure that resulted in the discovery of most cases was the notification by non-specialist doctors (46·62%), followed by voluntary presentation for examination (22·91%). This fact is connected with health education. Examination of contacts has resulted in the diagnosis of early cases, a fact worthy of comment.

II 16

Reduction in infectivity in patients undergoing treatment with sulphones

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The study covers the 11 years from 1957 to 1967. In this period, home treatment in graduated form was carried out until a total of 233 cases had been collected.

The average time in which these patients remained bacteriologically positive was 29 months; the number of contacts of these patients was 2,799.

During the same period 387 new leprosy patients were diagnosed; in 291 the source of infection was known, and in 96 not known. Of the 291 patients, 116 (or 40%) were among the contacts of the patients studied.

During the last 20 years, work has been in progress on the study of "chains of infection" as a function of time; up to now, 128 chains have been found in which leprosy had been transmitted to relations and friends, to a total of 734 cases (473 living and 261 dead). These chains were arranged in chronological order, the first beginning in 1899.

In order to carry out the investigation of these "chains", the Registry and Clinic documents were examined and the family visited in order to obtain accurate and complete information.

Of the 116 cases of leprosy occurring in contacts of the patients under study, 81 were in 51 chains which began before 1957 and in which the infected patients were known. The other 35 belonged to 11 chains which apparently started after 1957, but, investigated separately, resulted from other chains which had been initiated many years previously.

II 17

Epidemiology and control of leprosy in Cuba

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In this present work are analysed the epidemiological characteristics of leprosy in Cuba, which though being situated within a leprosy focus, present an endemic of moderate intensity with a national prevalence rate of 0·5.

We study the expansive potential of the disease, based on the cases already registered. The trend of new infections is more apparent in the age groups over 15 years. There were more males than females affected.

The principles underlying the leprosy control programme in Cuba are described, as are its essential features:

1. The abandoment of compulsory segregation.
2. The integration of the leprosy programme into the general public health programme.
3. Determined action in making epidemiololical surveys.
4. The promotion of health education.
5. The unitary concept of health.
6. The prevention and correction of deformities.
7. Social and economic rehabilitation.

The following are some of the activities carried out by the programme: control of patients; examination of contacts; examination of apparently healthly persons.

II 18

Mechanism of transmission of leprosy

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While working out the data regarding the spread of leprosy throughout the Astrakhan area and Karakalpak Autonomous Soviet Socialist Republic, we met with facts that contradict the established view about the importance of the skin in the transmission of leprosy.

1. Leprosy is said to be most prevalent in countries with a high humidity, but this assumption is not in accord with the view that leprosy is transmitted by direct contact with patients with leprosy. If this is so, environmental conditions are not important.

2. There was no correlation between shortening of the period of exposure to the source of infection and the incidence of leprosy.

3. There is a discrepancy between the high prevalence of leprosy in some populations (30 – 35%), and the widespread view that leprosy is but slightly contagious. The members of families having a member suffering from the lepromatous type of leprosy, and the children of leprosy patients living in leprosaria, may belong to such groups of high prevalence.

The frequency of transmission of infection may be appreciably greater than the clinical morbidity. The cases of latent, abortive, self-healing leprosy mentioned by many authors are indicative of it.

In the area of high prevalence of leprosy, the high rate of "child" infection is evident.

All these facts support Gromashevsky's standpoint (1941) about the importance of droplet infection in leprosy. This mechanism will assure the survival of *M. leprae* which would otherwise perish in the environment.

II 19

Accidental transmission of leprosy by blood transfusion in uniovular twins

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After making some observations upon the genetic and infectious factors in leprosy, we review the literature on accidental voluntary inoculations.

We record the case of two children aged three years, uniovular twins without family history of leprosy or contact with leprosy, who at the age of twenty months had severe gastroenteritis with dehydration. They were treated with three transfusions of whole blood obtained from a donor who was subsequently found to have lepromatous leprosy.

Both children simultaneously developed cutaneous lesions two years later. A study of these children revealed tuberculoid nodular leprosy in the first and tuberculoid leprosy in the second.

We make clinical comments on these interesting cases, stressing the lowering of body defence mechanisms at the time of the transfusion, the stimulating effect of the young age of the patients and the genetical factor in these univolular twins.

II 20

The oral route of transmission of *M. leprae*

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The author believes that the oral route of transmission of *M. leprae* is definitely possible for the following reasons:

1. *M. leprae* in active form have been discovered in the breast milk of a lactating mother suffering from highly lepromatous leprosy.

2. *M. leprae* have been discovered in the nipple secretion and of the hypertrophied mammary gland ducts of men with gynaecomastia and highly active and untreated lepromatous leprosy. This finding strongly suggests that the same histopathological picture would obtain in the mammary gland of a lactating mother suffering from lepromatous leprosy. Microphotographs will be shown in proof of these findings.

3. Innumerable *M. leprae* and many globi, most of the bacilli being in solid rod form, have been discovered in the nipple secretion of an elderly Nepali woman with advanced untreated lepromatous leprosy. A microphotograph with many bacilli in one field will be shown.

In addition, three microphotographs showing many bacilli and globi in the sputum of this woman will be shown to focus attenton on the fact that *M. leprae* can be present in the respiratory tract.

II 21

Modern epidemiology of leprosy: contribution of genetics

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The epidemiology of leprosy must in these days be considered in the light of two factors: the specific mycobacterium, and the individual predisposition, probably determined genetically. The mycobacterium must be combated at three points:

1. Medical personnel trained in the early diagnosis, systematic examination, and preventive vaccination by means of BCG of the whole population; clinical and immunological examination twice every year of all contacts; the rehabilitation of leprosy patients, and the consequent transformation of leprosy settlements into integrated rehabilitation units.

2. The education in health matters of patients and their contacts, by utilization of all possible mass media of communication.

3. Scientific research into especially the matters of genetic predisposition; utilizing a new epidemiological clue, i.e. dematoglyphics; and search for chromosomal aberrations. There is a statistically significant increase in finger-print ridges in women with lepromatous leprosy, and also an increase of the proximal triradiae t′ and t″ in patients with lepromatous leprosy and their family contacts.

Genealogical trees should be examined in order to discover any possible transmission of significant characteristics. Genetic markers (such as taste-testing with phenyl-thiourea, and determination of blood groups) should also be utilized in the investigation of genetic factors concerned in susceptibility to leprosy.

OPHTHALMOLOGICAL ASPECTS

III 22

Ocular leprosy: symptoms, signs and prognosis

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In leprosy, ocular involvement is probably more frequent than in any other general disease.

The incidence varies greatly with different observers. Probably 25% of all patients eventually show ocular involvement. Eye signs are quite different in the two main types.

Non-lepromatous leprosy shows no direct infiltration into the globe; vision is threatened by the complication of lagophthalmos; exposure keratitis, corneal ulcer, hypopion, iritis, endophthalmitis, perforation, phthisis bulbi.

Lepromatous leprosy shows direct leprous infiltration of the globe; nodular scleritis, superficial punctate keratitis, interstitial keratitis, iritis, choidoretinitis.

Prognosis: 115 leprosy patients showing facial lesions (66 non-lepromatous and 49 lepromatous) were examined and recorded in detail. Nine years later, 25 of them (14 non-lepromatous and 11 lepromatous) were traced and re-examined. In spite of treatment with sulphones during the immediately preceding 2 – 6 years before re-examination, 4 patients with non-lepromatous leprosy developed exposure keratitis, and 5 with lepromatous leprosy developed iritis. The importance of accurate detailed examination of the eyes and the necessity of local ocular treatment, in addition to general treatment, is emphasised.

III 23

Early ocular changes in leprosy

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This paper represents a rough analysis of the biomicroscopic findings in the eyes of 200 patients admitted since 1945 and followed at Carville. In the early years of this period, routine eye examinations were made at least once a year. Since 1955, they have been made quarterly or more frequently.

The paper also gives the overall impressions gained during a survey conducted at the Schieffelin Leprosy Research Hospital, Karigiri, South India, in 1962. This entailed recording the biomicroscopic findings in the eyes of 500 patients with untreated leprosy. If did not include follow-up examinations.

The object of the analysis is to answer the following questions:

1. How soon after skin manifestations do ocular changes become evident?
2. May these changes precede skin lesions?
3. What are the commonest early ocular changes?
4. How does the picture of ocular changes relate to the patient's resistance to the disease?
5. How far are the changes reversible?
6. How far may regular biomicroscopic study of the eyes help in monitoring the progress of patients under therapy?

III 24

The diagnosis and management of ocular leprosy

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Diagnosis

It is stressed that the ophthalmologist is often in the position to make a firm diagnosis of leprosy in advance of a general clinical diagnosis. His chances of doing so are materially helped by access to sophisticated equipment, e.g. a corneal miscroscope. Normally a cumbersome affair, the development of a light-weight portable model represents a notable advance. The physical signs of ocular leprosy are sub-divided into non-specific manifestations and those which are only found in leprosy.

Management

1. Timely tarsorrhaphies should prevent the loss of eyes from the effects of exposure and/or neuro-paralytic keratitis.

2. Surprisingly, leprous eyes stand up well to necessary eye surgery, good results being reported following cataract, glaucoma, corneal graft and even retinal detachment operations.

3. The great importance of various forms of iritis and iridocyclitis is emphasised. This feature of the disease has become particularly marked since the introduction of newer and more powerful drugs for the treatment of leprosy. The reasons for this are discussed and reference made to the beneficial effects of a complete or full iridectomy in cases where pupil *seclusion*, iris *bombé* and secondary glaucoma are present or threatened. It is concluded that the modern treatment of leprosy must include the services of an ophthalmologist familiär with ocular leprosy, otherwise many patients are only going to be saved from death or mutilation at the cost of blindness.

III 25

Blindness in leprosy patients The work of the Royal Commonwealth Society for the Blind

H. RIDLEY
The
Royal Commonwealth Society for the Blind,
London

The Royal Commonwealth Society for the Blind is interested in the treatment and prevention of all diseases likely to lead to serious visual impairment throughout the British Commonwealth. Among such diseases is leprosy, in which the eye lesions are not so much complications as manifestations of the disease. Whilst leprosy can affect the eyes, either by direct invasion of the lepra bacillus, or indirectly by causing a nerve palsy, many eyes are affected in both ways.

Many leprosy patients go blind from corneal opacity, from cataract and secondary glaucoma. They are segregated and well cared for in general, but their eye troubles do not always receive regular and adequate treatment.

The Royal Commonwealth Society for the Blind has sent surgical teams to various parts of the world; in recent years, one team has gone to Malaysia and Hong Kong, and another to Guyana and other Caribbean countries, primarily with the aim of treating blind leprosy patients.

A general survey of the ocular conditions found and the methods of treatment will be discussed.

III 26

Leprosy of the eye Present status and future challenge

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Lepromatous, tuberculoid and indeterminate forms of eye manifestations of leprosy will be illustrated with 35 mm. Kodachrome slides.

Recent advances in diagnostic techniques and therapy will be suggested in reference to ocular manifestations of leprosy.

III 27

Ocular leprosy following sulfonamide treatment

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The author will show that current treatment of leprosy and plastic surgery make possible the prevention and treatment of ocular leprosy. The lesions of lepromatous leprosy of the eyeball are avoidable nowadays, with appropriate treatment at the proper time.

The eye lesions associated with tuberculoid leprosy and indeterminate leprosy are those caused by frequent attacks of facial neuritis. This condition, with its numerous consequences, constitutes a difficult problem. Although demanding skill and patience, and with results that are not always permanent, plastic surgery offers reasonable treatment of the disastrous effects caused by eyelid paralysis.

Perineural injections of hydrocortisone are useful in acute leprosy neuritis of the facial nerve.

The author describes briefly the surgical methods used at the Sanatorio Santa Isabel and at the Hospital de Recuperação do Hanseneano, do Departmento de lepra of the State of Minas Gerais (Brazil), and will show coloured transparencies of some of the treated patients.

III 28

The conjunctival flora and that of the tears, conjunctivitis and some other diseases of the anterior segment of the eye in a patient with Hansen's disease

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In this work, we lay special stress on the study of the conjunctival flora and that of the tears in a group of patients with Hansen's

disease, and we compare the results obtained with those of the same investigation performed on healthy people, some living with them and some not. We use simple methods, within the competence of practitioners not specialized in laboratory techniques, because we think that this investigation may serve as an indication for a later, more thorough bacteriological examination (and which may be the subject of a further communication).

Our extensive experience in the recognition and treatment of ocular lesions of leprous origin, enables us to establish the probable *low incidence* of diseases of other etiology resembling leprous conditions of the eye, such as conjunctivitis. It is these ideas that have motivated this communication. Similarly we are also concerned with an investigation of the coexisting non-specific corneal processes, trying to differentiate these from the typically Hansen-like keratitis.

III 29

Ocular lesions in leprosy

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This paper is based on a study of nearly 2,000 leprosy patients.

In non-lepromatous leprosy, facial paralysis (unilateral or bilateral) occurs, with resulting recurrent ulceration from corneal anaesthesia.

A quarter of all patients with lepromatous leprosy and one half with advanced disease develop eye complications. Madarosis occurs late. A vascular pterygium results from lepromatous infiltration. Lachrymal sac infection is not uncommon. The sclera may be the seat of a localized leproma, and a more diffuse chronic scleritis may occur. The cornea is also involved.

Acute and subacute iritis, followed by the usual sequelae, are common and serious. In contrast, the incidence of optic atrophy is low, but direct leprosy involvement of the posterior segment is noted.

The treatment of ocular lesions in leprosy follows the usual pattern of treatment when the cause is other than leprosy. Temporizing and protective measures for the anaesthetic cornea may be supplemented where necessary by operations (tarsorraphy, temporalis transfer).

Scleritis is amenable to local cortisone therapy – instillation, or subconjunctival injection.

Dapsone should be continued, in low doses, during an acute ocular episode. Cold eye surgery (e.g. cataract extraction) may be safely performed when the Bacterial Index has been negative for 3 months.

EXPERIMENTAL LEPROSY - BACTERIOLOGY

IV 30

Methods for the study of *M. leprae* by the inoculation of mice in the foot pads

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Following inoculation into the foot pad of a normal mouse, *M. leprae* multiplies with great regularity under suitable conditions which can be described. The bacillary growth curve consists of a lag phase, a logarithmic phase, and a plateau phase, and advantage can be taken of the regularity of the curve to measure relatively small effects. The end of the logarithmic phase, and thus the onset of the plateau phase, is apparently a function of the immune response in the normal mouse to a bacterial population of about 10^6 bacilli and at this time many *M. leprae* are killed. In a mouse that has been well vaccinated with BCG, or with oil-treated BCG cell walls, the immune response is triggered by a lower bacterial population and the plateau level is 10- to 100-fold lower. There are several methods that may be employed to monitor growth of *M. leprae* in the foot pad, and their relative advantages will be discussed.

IV 31

Recent advances in the transmission of human leprosy to mice

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The long-awaited successful transmission of human leprosy to animals was first achieved by Shepard in 1960 by the inoculation of *M. leprae* into the mouse foot pad. Unfortunately, bacillary multiplication was limited and remained localised to the site of inoculation, thus restricting the scope of this experimental model. Therefore methods were used to enhance the infection on the assumption that the limiting factor had an immunological basis.

This assumption has been proved correct, since a progressive infection, eventually reproducing the characteristics of lepromatous leprosy in man, has been obtained in mice (strain CBA) by prior obliteration of their defence mechanisms by thymectomy followed by total-body irradiation (900 r). The essential methods will be described.

Thymectomy plus irradiation increases significantly the multiplication of *M. leprae* inoculated, both locally and systemically. Inoculation of *M. leprae* into the foot pads or ears of mice yield 100 - 1,000 more bacilli locally in treated than in normal animals, with spread to other tissues and, morover, intravenous inocula produce heavy and generalised infections, particularly involving foot pads, ears, nose and tail skin. The application of this new experimental model for studying the bacteriology and immunology of leprosy will be discussed.

IV 32

M. leprae in atrophic mouse limbs Survival of *M. leprae in vitro*

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Difficulties encounted during 5 years' passage and isolation of *M. leprae* in mouse foot pads were attributable to accidental loss of inoculated mice from intercurrent disease in inoculated animals (mostly ectromelia).

In view of the findings of Rees and co-workers that multiplication of *M. leprae* can or does occur in muscle cells or muscle-associated cells of the mouse foot pad, it was thought that cutting of sciatic nerves (which is followed by atrophy of the corresponding limb) could influence the multiplication of *M. leprae* in the mouse foot pad. These experiments were made and will be discussed.

The harvest of *M. leprae* from mouse foot pads was suspended in different culture media and their viability assessed after different time intervals, either by subinoculation in mouse foot pads or by evaluation of solid staining bacilli.

Through inoculation into foot pads, the survival of some *M. leprae* could be demonstrated over a period of 4 months.

In the best conditions, counts of solid staining bacilli revealed a sharp fall between the 3rd and 4th months.

IV 33

On the results of experimental infection of mice with material taken from leprous patients

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1. Rather important but not yet solved in the problem of leprosy is the question of finding an animal subject to experimental infection by *M. leprae*.

2. While infecting mice in the foot pad, according to the procedure of Shepard, and also by means of a combined method, we have definitely demonstrated reproduction of bacilli in the place the material was injected (the foot pad).

3. Multiplication of mycobacteria was obtained both in the mice injected with the material taken from lepromatous patients, and also in those injected with material taken from tuberculoid patients and containing very few bacilli.

4. From the animals infected for the first time, we have obtained transient infections with a shortened period of reproduction of mycobacteria in infected animals.

5. The characteristics of mycobacteria in the infected experimental animals and their identification with *M. leprae* are discussed.

IV 34

The physiological peculiarities of rodents favouring successful inoculation with *M. leprae*

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1. Successful inoculation of *M. leprae* obtained from lepromatous tissue or exudates into different species of laboratory and wild rodents is now routinely achieved. This success is connected with some physiological peculiarities of these rodents, or some external conditions; both of these factors act by lowering the natural resistance of rodents to this bacillus.

2. The temperature of peripheral tissues (foot pads, ears, testicles) is lower than that of internal organs. The success of experiments with golden hamsters is connected with the imperfect thermo-regulation of this hibernating species. Some workers have found that some specific reactions of Tamarix gerbill to inoculation of lepromatous material in the winter months, are related to abrupt seasonal changes in thermo-regulation. The low temperature of body surface is connected with the intensity of metabolic changes in these tissues, and a marked difference is evident in the chemical structure of fat and exchange of fatty acids.

3. The changes in the fat metabolism of rodents connected with their feeding with pro-oxident diets or with addition or deficiency of tocopherol (vitamin E), also favours the inoculation of rodents with *M. leprae*. In white rats and Tamarix gerbills, multiplication of *M. leprae* was obtained when tocopherol accumulated in the animal body, which lowered the intensity of interaction between microbe and host tissues. The pro-oxidant diet, on the contrary, was evidently the cause of very rapid interaction of *M. leprae* and animal tissues with not only allergic reactions on the skin, but also with the destruction of *M. leprae*. The changes in content of the tocopherol in the organism of mammals is the cause of the fluctuation of intensity of exchange, and changes in the permeability of the cell membranes.

In the black laboratory mice and in the Tamarix gerbills, there are sudden changes of the tocopherol content of the body, but in white mice, as well as in the Meridian gerbill (both species that cannot be infected with *M. leprae* in the same conditions) the level of vitamin E during the year remains constant.

IV 35

A possible role for anti-lymphocytic globulin in the enhancement of leprosy infections (*Myco. lepraemurium* and *Myco. leprae*) in the mouse

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The way in which anti-lymphocytic globulin (A.L.G.) reacts on immune processes is uncertain. This agent significantly enhanced the susceptibility of mice to infection with either *M. lepraemurium* or *M. leprae*. Although unrelated, both causative bacteria are obligate intracellular parasites. The histological picture of such infected tissues provides evidence for a possible mode of action of A.L.G.

Briefly, amongst the lymphoid organs of mice heavily infected with murine leprosy, a large proportion of parasitised bi-nucleate macrophages were seen, especially within the bone marrow, and specially when treated with A.L.G. These abnormal cells were not thought to contribute towards giant cell formation. Indeed giant cells were rarely found.

In addition, localised *M. leprae* lesions induced in the paws of thymectomised mice administered A.L.G. were almost devoid of lymphocytes, but macrophages were abundant. Besides being within these macrophages, clusters of mycobacteria were located in most plantar tissues including sebaceous glands, striated muscle fibres and nerves. Thus, although the lesions were microscopic they possessed features of lepromatous leprosy.

In conclusion, cell-mediated immunity rather than humoral-mediated immunity is important for the host's defence against both the foregoing types of leprosy.

IV 36

Attempts at experimental transmission of leprosy to terrestrial Chelonia from the Amazon region, Brazil

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Following a series of attempts at experimental transmission of leprosy in animals, the writers report the results of an inoculation of *M. leprae* to terrestrial chelonia which belong to the *Kinosternon scorpioides* (Mussuan) and *Geoemyda punctularia* (Perema) which live in the Amazon region of Brazil.

The inoculum was a bacterial suspension very rich in acid-fast bacteria obtained from fresh lepromata in untreated cases. Each animal was given 0·2 ml once, by subcutaneous injection into the hind foot pad.

The assessment of the results was made by periodic bacterioscopic and histopathological examinations of smears and sections of the inoculation site and internal organs, from 4 months and up to 2 years and 8 months after inoculation in the peremas and up to 4 years and 5 months in the mussuans.

In the mussuans (*Kinosternon*), notwithstanding occasional findings of acid-fast rods in the inoculation site up to 8 months after inoculation, no granulomatous lesions which could be related with the development of *M. leprae* were to be found.

In the peremas (*Geoemyda*), several lymphocytic inflammatory foci and some small granulomatous lesions with histiocytic structure have been found both in the inoculation site and in the liver.

Evidence of nerve involvement in a few of these lesions was seen as well, in spite of the lack of acid-fast organisms.

These results suggest further investigation of these species and of others not previously used in experimental leprosy research, as the problem of leprosy transmission has not yet been solved.

IV 37

Attempt to cultivate *M. leprae* in cultures of fibroblasts derived from the skin of lepromatous leprosy

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Because cell species specificity might be an important factor for parasitization of *M. leprae*, we chose a line of human diploid cells from lepromatous leprosy.

The author reported at the 8th International Congress on Leprology, 1963, that the fibroblasts derived from the skin of lepromatous leprosy patients were considered to be adaptable for the host cells to intracellular parasitization of *M. leprae*.

The cell strain is capable of continuously transplantable growth in a period of around one year. In the past 6 years, 23 cell strains were obtained from the skin of different lepromatous leprosy patients and employed for experiments.

By repeatedly subculturing the infected fibroblasts at intervals of 30 to 40 days, the growth of *M. leprae* within the cell was studied for a period of more than 5 months.

Enumeration of the bacilli was carried out at the time of each subculture by means of counting bacterial numbers inside cells and the number of acid-fast bacilli in smears of the bacillary suspensions, which were prepared by exposing the cells to sonic vibration.

At the end of 3 months, elongation of the bacilli was frequently observed, and bacterial increase of 30- to 46-fold was observed during a period of 130 days.

There was no growth of acid-fast organisms in bacteriological media inoculated with organisms harvested from the culture.

IV 38

The inoculation of *M. leprae* in the synthetic media enriched with mycobacterial extracts, nocardamin and ferrioxamin

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The purpose of the work is to relate the attempts made at Instituto de Leprologia G.B. to cultivate *M. leprae in vivo*.

After the lack of success in cultivating *M. leprae* in different strains of tissue culture cells, we incubated *M. leprae* in media enriched with several growth factors. The medium of D'Arcy Hart was enriched with atypical mycobacteria; filtrates of the cultures of several atypical mycobacteria; filtrate of the cultures of several nocardia; solution of ferrioxamina B.

An attempt of symbiosis was made in Löwenstein medium with some atypical mycobacteria.

All results were negative.

IV 39

Pedigreed stocks of *M. leprae* as baselines in cultivation trials

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Minimal requirements for proper cultivation trials are: (a) aseptic, metabolically active suspensions that are adequate for a series of comparable experiments and (b) a "reference" stock for rechecking unusual observations. Current proposals to expand cultivation trials in places remote from the sources of inoculum are frustrated by the fact that the investigator is unable to control the selection of patients, the sterilization of skin, the size of specimen, the asepsis of surgery, the conditions of period of shipping, or the time of arrival. Even a modest ratio of contaminated lepromas prevents "pooling" of the required volumes. Decontamination yields flocculated tissue suspensions and prevents pipetting uniform aliquots.

The method to be described eliminates saprophytic mycobacteria and other contaminants, prevents flocculation of tissue components, and maintains the metabolic activity and infectiousness of a model organism, *M. lepraemurium*, for many months.

IV 40

The survival of "cool-dried" *M. leprae*

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A suspension of *M. leprae* harvested from mouse foot pads was diluted in (a) glass-distilled water containing 0·1 % bovine albumin, or (b) a sucrose-potassium-glutamate (S.P.G.) medium to which 0·1 % bovine albumin was added. Aliquots of the diluted suspensions were distributed in glass ampoules, cooled in melting ice, and dried *in vacuo* without being allowed to freeze. The dried suspensions were stored at 4° and at 20° C. and sampled for viability at 4 days and at 1, 6 and 15 months; each sample was reconstituted to the original volume and standard amounts inoculated into the foot pads of groups of mice. The viability of these test suspensions was assessed by comparing their rates of growth in the mice

(expressed as the generation time) with those of aliquots of the original liquid suspensions which had similarly been inoculated into mice at the start of the experiment.

These results showed that bacilli dried from albumin solution retained viability for only one month. In S.P.G. albumin medium, full viability could be preserved for 15 months, though irregularly. Storage at 4° showed no advantage over storage at 20° C. The findings have implications both for the preservation of leprosy bacilli for laboratory use and for their survival in dried secretions, and further investigations of this kind seem justified.

IV 41

M. leprae: Relation between morphology and viability

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Rapid measurement of viability has special value in the case of *M. leprae*, in laboratory research as well as in assessment of the patient's chemotherapeutic response. A proposal that only solid (completely staining) bacilli are viable was tested in an earlier study (*J. Bacteriol*, **89**:365, 1965) on accumulated laboratory experience. We concluded that some dead organisms were being scored as solid, and therefore increased the strictness of our definition of a solid bacillus. Enough experience has now been accumulated for an assessment of the new definition. The principle test was to correlate the average rate of bacillary growth between inoculation and harvest with the proportion of solidly staining bacilli in the inoculum. It was found that the rate of growth does not vary now with the proportion of solid bacilli, thus providing strong evidence that the present definition is correct. Analysis showed that the growth of *M. leprae* was more consistent when the inoculum contained more than 100 solid bacilli. Also it could be seen that the incubation period (time for appearance of acid-fast bacilli in inoculated feet) probably never exceeded 12 months.

IV 42

Purification and identification of *M. leprae* by the method of counter-current distribution in polymer two-phase system

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For collection and identification of *M. leprae* (murine leprosy bacilli) obtained from leprous lesions, it was found that the techniques of counter-current distribution in polymer two-phase system were fairly effective.

Polymer two-phase system composed of dextran and polyethyleneglycol, was very suitable for determining the viability of micro-organisms and highly sensitive for their differentiation. (This method was developed by Dr. Albertsson).

According to the counter-current distribution in this system, the bacilli and tissue components were clearly demarcated in different tubes.

The bacilli obtained from subcutaneous, lymphatic, and spleen nodules showed the same distribution pattern with a single high peak, but the pattern of the bacilli obtained from liver nodule had more than one high peak.

There were distinctly different distribution patterns between *M. leprae* and other mycobacterial species.

These results will be reported, together with electron microscopic observations.

IV 43

Metabolic and biologic tests on mycobacteria once labelled as leprosy bacilli

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Among mycobacteria listed in Bergey's Manual of Determinative Bacteriology, 7th edition, 1957, dopa-oxidation is characteristic of *M. leprae*. The possibility that this enzymatic activity results from absorbed human enzyme has been excluded by two observations.

1. Leprosy bacilli obtained from infected human spleen oxidize dopa. Human spleen tissue itself has no phenolase activity.

2. The dopa-oxidase of the leprosy bacillus and of mammalian tissue can be distinguished by differences in substrate specificity.

It seemed of interest to subject mycobacterial "species" selected from the Catalogue of Cultures, 7th edition, 1964, American Type Culture Collection (ATCC) and believed at one time to be the leprosy bacillus to the dopa-oxidase and the mouse foot pad tests. Also tested in the same way were some mycobacteria listed in the Catalogue, isolated originally from ticks experimentally infected with lepromatous material. None of the 15 mycobacterial "species" from the ATCC oxidizes dopa even in masses far in excess of those of *M. leprae* that regularly give a positive test. Permeability barrier could be excluded since crushed bacilli gave the same results. There was no indication of multiplication in the mouse foot pad until up to six months after inoculation of from $9{\cdot}4\times10^3$ to $28{\cdot}0\times10^3$ bacteria. These cultivatable mycobacteria did not resemble leprosy bacilli in these two respects.

IV 44

Factors affecting elongation of *M. lepraemurium in vitro*

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Elongation of *M. lepraemurium in vitro*, which was first described by Hart and Valentine, was confirmed by the slide culture method. This slide culture method which has been employed for early growth of *M. tuberculosis in vitro* eliminates the disadvantages involved in the original method, for observing elongation of *M. lepraemurium*. By this method, the factors essential for elongation of the bacilli *in vitro* were studied; the results obtained demonstrated that the three following factors were needed for elongation phenomenon:

1. The obligate acidity of the medium containing protein; the result reported by Hart and Valentine was strongly supported.

2. Freshness of the materials; the bacillary materials tested for elongation should be used as soon as possible after harvest from the mouse tissues infected with the bacilli.

3. Cultivation under low relative oxygen tension; elongation occurred under the appropriate low oxygen tension more consistently and to a greater extent than under high oxygen tension.

Problems related to certain characteristics of acid-fast bacilli will be discussed.

IV 45

Further studies on morphological changes of *M. lepraemurium* grown in macrophage cultures

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A preliminary study (1968 Annual Meeting of American Society for Microbiology) presented observations on morphological changes in short form *M. lepraemurium* during growth in cultures in mouse peritoneal macrophages. We observed that non-solid bacilli increased during bacillary multiplication and that most of the short, solid organisms showed elongation. Furthermore, autoclaved *M. lepraemurium* showed an increase in non-solid organisms without a simultaneous increase in the number or length of the organisms.

In the present study, long form organisms obtained from a serially transferred subculture were used. The organisms showed an increase in length of 0·9 μ in 3 weeks, and an increase in number of 55-fold in 6 weeks. The number of non-solid organisms increased from 47% to 68%, and the length of non-solid organisms increased 0·7 μ in 2 weeks. These results indicate that long bacilii also show the emergence of non-solid forms with simultaneous elongation during multiplication.

It may be concluded that an increase in number of non-solid bacilli was observed in the growth phase of *M. lepraemurium* in macrophages, regardless of the size of organisms at the time of infection.

IV 46

Placental infection in the foetus of pregnant murine leprous mice

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The authors discovered acid-fast bacilli, which failed to grow in culture media, in young normal mice, even as young as 3 days. In addition, acid-fast bacilli were found in 14 of 149 foetus of 20 healthy pregnant mice. The following experiments were carried out. Two different groups (A and B) of mice were kept together in the breeding cages. The first group (A) was composed of females infected with murine leprosy, and normal males; the second group (B) was composed of normal females and males infected with murine leprosy. Pregnant mice were taken from both groups A and B, autopsied, and carefully examined. When the female mice of group A and B were delivered of offspring, they were also examined. In the second experiment normal females (in group B) and normal males (in Group A) which had been kept together with leprous mice for a few months were examined. Both the foetus and also the offspring of these females were investigated for the presence of acid-fast bacilli. The chief result was as follows: 12 of the 41 leprous females became pregnant, and acid-fast bacilli were found in 15 of their 77 foetuses.

IV 47

Studies on filterable form of murine leprosy bacillus

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During experiments, in which a diffusion chamber prepared with Type HAWP Millipore filter (Pore Size 0·45μ ±0·2μ) and filled with murine leprosy bacillus, is implanted intraperitoneally in the mouse, it was found that acid-fast organisms were often present in the cells of the membrane surrounding the diffusion chamber. Studies were therefore conducted to ascertain if there was a filterable form of murine leprosy bacillus.

A suspension of murine leprosy bacillus was filtered through a Type HAWP Millipore filter and the filtrate was inoculated subcutaneously in the back of mouse. Scattered acid-fast organisms were observed after 1 month, and numerous acid-fast organisms were seen after 3 months in the spread preparations of the subcutaneous tissue of inoculation site, and at 4 months a murine leproma formed at the site.

With the filtrate obtained by filtering through a Type GSWP Millipore filter (Pore Size 0·22μ ±0·2μ), a small number of granular and rod-shaped acid-fast organisms were noted at the inoculation site after 1 month, but compared to the filtrate prepared with the Type HAWP, a definite difference was apparent.

The results suggest that minute infective particles which will pass through the regular bacterial filter may be present in the lesion of murine leprosy as suggested by Markianos (1929).

IV 48

Establishment of mouse-adapted strain of human leprosy bacillus

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Numerous reports have been published that proliferation of the human leprosy bacillus in the foot pad is inhibited by the administration of DDS or inoculation with BGG. Though the findings do not give concrete evidence that the proliferating organism is truly the human leprosy bacillus, it cannot be denied that the foot pad inoculation method is a useful method for experimental studies on leprosy.

It is regrettable that the results obtained in our laboratory by this method have been very inconsistent and that regular results have not been obtained. The attempt is, therefore, being made to obtain a strain of human leprosy bacillus with which proliferation will always take place when cultured according to the same method, by adaptation in the mouse.

The results obtained up to the present time are as follows. From material obtained from 15 patients in Japan, passage of 2 strains has been successful up to the third generation and 4 of 5 strains made available by Shepard have been successfully passaged for more than 3 generations in the mouse. It is believed that further passage of strains, that have been passaged in the mouse for more than 3 generations, is possible under the same conditions. The establishment of a mouse-adapted strain appears highly feasible in the light of these findings.

It has been found, however, that there were acid-fast bacilli of about 10^4 in the second generation when an emulsion prepared from the foot pad of an untreated healthy control mouse was inoculated. This is an important finding and studies are being carried out in order to explain this.

VI 49

Studies of morphology of the mycobacteria

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Knowledge of the morphology and mode of reproduction of the mycobacteria is fundamental to the cultivation of *M. leprae*. Most of the existing knowledge is based on studies using the Ziehl-Neelsen staining or modifications of this method. The chemical and physical effects of this technique are harsh and, very little is known regarding its effect on the natural morphology of the organism.

Additional information has been obtained using the electron microscope, but again the preparative procedures are harsh. In addition, the emphasis of electron microscopy is directed at those bodies which are indicated as being comparable to the organisms demonstrable by Ziehl-Neelsen technique.

The studies reported here were undertaken to investigate the natural morphology of the mycobacteria. Wet-mount specimens of mycobacteria were compared with equivalent area-volume Ziehl-Neelsen stained smears. The wet-mounts were observed with oblique lighting of vital stained suspensions as well as with phase-contrast, polarized light and dark field microscopy of unmodified suspensions. Photomicrographs were made of pertinent subject matter.

This report demonstrates the comparative morphology of stained *vs.* unmodified wet-mount suspensions of pure cultures of NQ, R1Rv and *M. tuberculosis*. Tissue suspensions of *M. lepraemurium* and *M. leprae* are also included in the comparison.

IV 50

The inoculation of *M. leprae* in the muscles of mice and rats. Bacteriological and histopathological study

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After the initial finding that when *M. leprae* were inoculated in animals by different routes, bacilli were found more easily in the muscular tissue, systematic inoculation by this route was made over several years in different animals; the bacteriological and histopathological findings are recorded and discussed.

More than 100 mice and about 20 albino rats were inoculated by the intramuscular route with *M. leprae*. After intervals of 4 – 6 – 8 – 10 – 12 months, and some of them after a period above a year, the animals were necropsied. The muscles, liver, spleen and regional lymph nodes were examined. In the histopathological examination, infiltrate was seen in muscle, and sometimes in other neighbouring tissues. The infiltrate was formed usually by mononuclear cells with hyperchromatic nuclei, lymphocytes, histiocytes, fibroblasts preferentially around capillaries, nerves and in the interfascicular space.

Not always, these infiltrates were accompanied by the presence of acid- and alcohol-fast organisms.

The authors suggest that myoglobin, a carrier of iron in the muscle, may be a growth factor for *M. leprae*.

IV 51

Acidophil properties of purified suspension of *M. leprae* and *M. lepraemurium*

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It has been found in two independent laboratories that *M. lepraemurium* retains infectiousness for longer periods when incubated at pH 8·0 than at pH 5 to 7. Further, maximal hydrogen transfer capacity was obtained at slightly alkaline pH, with a second preference at an acidic value. The following working theory was therefore tested. Non-cultivability is not necessarily due to a lack of essential nutrients in the medium or metabolic deficiency of the micro-organism, but because of unusual acquired characteristics and/or transfer of inhibitors from the chronically infected host into the test media.

In the course of such studies, it was found that *M. lepraemurium* isolated from not more than 3 months old subcutaneous granuloma of rats and inoculated into Dubos liquid medium (without Tween and serum albumin but with glycerol 0·6% added and adjusted to pH 8·0) remained infective *after* 40 *dayss' incubation at* 37°C. Bacilli lost their infectiousness at pH 3, 5, 6 and 7. When bacilli were incubated on agar slopes, infectiousness was maintained after 40 days at pH 3·0 and 8·0 but not at pH 5·0, 6 and 7 when incubated at 37°C and also at 34°C. Acid-fastness at 40 days was estimated as being most marked when the bacilli were kept at 34°C on agar slope, at pH 3·0. The observations required to investigate whether *M. lepraemurium* is not a Mycobacterium acido-philum. The probability of such an adaptation in the host is not excluded, considering the fact that the pH of the storage granules in the macrophages, where *M. lepraemurium* multiply in the host, is 3·0 or less, thus permitting an acidophilic adaptation.

A culture filtrate of *W. perfringens* at pH 3·0 selectively digested cellular and subcellular elements as well as macro-molecules of human and rat leprosy biopsy material without affecting the staining properties of both bacilli and the infective activity of *M. lepraemurium*. This technique permitted the preparation of purified suspensions.

IV 52

Studies on the cultivation of *M. leprae*

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During attempts to culture leprosy bacilli, it was not uncommon to observe some colonial growths on the media used. Most were merely "passenger" bacilli, but there was a group showing a remarkable pleomorphism: e.g., KN-1, KN-2, KN-3, etc. These are all acid-fast bacilli, but they possess differing characters.

Adopting a working hypothesis that these strains might be "the variants" and have some metabolic relation to leprosy bacilli, we attempted to isolate a growth-promoting factor from these strains.

Factor KN-1, extracted with alcohol from KN-1 culture, possesses such an activity, but this is insufficient for the growth of *M. leprae*.

Factors KN-2 and KN-3 are more effective. After inoculating the bacilli obtained from human leprous nodule on to the appropriate medium, and adding Factors KN-2 and KN-3, the slopes were incubated at 27–28° C for 2 weeks; flat and white colonies were observed.

These colonies are transplantable on the special culture media used, but they do not grow on conventional media. Each bacterium in these colonies shows a close morphological resemblance to *M. leprae*.

IV 53

Phenoloxidase of *M. leprae* and effect of inhibitors on the enzyme

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M. leprae separated from infected human tissues oxidizes a variety of phenolic compounds. This activity of the bacillus was similar to the enzyme of plant origin, and distinct from mammalian phenolase, where the substrate specificity is restricted. However, the products formed in the oxidation of phenolic substrates by *M. leprae* appeared to be o-quinones; but the plant enzyme gave rise to p-quinones.

The results revealed a highly specific metabolic property in *M. leprae*.

Several inhibitors of phenoloxidase were screened, initially on the enzyme from mammalian and plant sources. Effect of diaminodiphenyl sulfone on phenoloxidase of the bacillus was also tested. Since *M. leprae* possesses a characteristic phenolase activity, nontoxic inhibitors of the enzyme might be of value in developing a rational approach to chemotherapy of the disease.

IV 54

M. leprae and *M. tuberculosis* – bacilli with a common origin

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Having worked at Japanese Leprosaria for 45 years, as the result of my investigations I have reached the conclusion that *M. leprae* amd *M. tuberculosis* are different types of bacillus having a common origin.

Experimental evidence

1. Increasing of lepra bacilli in human leproma tissue by potato cultivation.

2. Mice experiments with these increased bacilli.

3. Acid-fast bacilli, separated from human leproma. Although the patients were diverse and the material was taken at different times, the characters of the bacilli are the same.

4. Skin reactions and serum reactions with these separated bacilli.

5. *M. tuberculosis* came to resemble *M. leprae* in the chicken experiments. In these cases, in spite of the proof that *M. tuberculosis* is active, the guinea-pig test was negative, and the bacillus could not be cultured again.

6. Experimental nodules of the chicken with cultured bacilli.

7. Rat experiments with these cultured bacilli.

Conclusions

1. I think that *M. leprae* and *M. tuberculosis* have the same origin, but that the normal type of *M. leprae* is smooth, whereas the normal type of *M. tuberculosis* is rough.

2. It is reasonable to find that *M. leprae* is not pathogenic for the guinea-pig, but that *M. tuberculosis* is pathogenic in this test. This differential test is, I believe, mistaken.

3. The opinion that acid-fast bacilli in human peripheral nerves are always *M. leprae*, and not *M. tuberculosis*, is, I think, mistaken.

PHYSIOTHERAPY AND PROSTHESES

V 56

The role of physiotherapy in a control project

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A leprosy control programme was started in 1962 in Pogiri, Andhra Pradesh, India, by the Danish Save the Children Organisation, with technical assistance of WHO. At present the population covered totals 1½ million, with 28,712 patients, of whom 6,851 (24%) have anaesthetic feet.

In the control scheme, a physiotherapy department has been incorporated, the main activities of which are carried out in the field and consist of repeated visits to clinics, during which Plaster-of-Paris casts are applied for clean plantar ulcers, and long leg plaster casts for early drop feet.

Of 549 plantar ulcers treated in this way, and observed for at least one year, 330 (60%) did not recur, while 219 (40%) recurred, most frequently within 3 months after removal of the plaster cast.

After application of a long leg plaster cast for 52 drop-feet, 35 showed satisfactory improvement for at least one year.

Beside the field activities, the physiotherapy department treats all patients admitted to a 50-bedded hospital, intended mainly for the treatment of patients ill with acute phases of leprosy. The most commonly applied techniques are: oil massage, exercises, wax baths and electrical stimulation. Pre- and post-operative physiotherapy treatment is given, but no surgery is done in the centre, the patients being referred to an orthopaedic surgeon in the neighbourhood.

V 57

Prosthetics for leprosy patients

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The need for a fully-skilled prosthetist as a member of the leprosy rehabilitation team is discussed. The prosthetist need not, and in fact should not, concentrate only on leprosy. The experience he gains from treating other amputees can be of great use to him when fitting leprosy patients. The designs of limbs used for anaesthetic stumps need not be different from the types fitted to patients who retain their sensation. The only special requirement in fitting anaesthetic stumps is a high degree of accuracy in socket shape and a careful control during the fitting and walking training.

The various designs and types of limbs are demonstrated together with indications of their suitability for different types of stumps.

The use of the patella tendon bearing shell for patients with badly deformed feet in whom footwear does not prevent re-ulceration, is shown.

The use of the immediate post-operative fitting of a prosthesis for patients with anaesthetic stumps, is considered.

V 58

Pre- and post-operative physiotherapy in leprosy

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This paper stresses the efficacy of modern techniques of physiotherapy treatment in leprosy, notably in the case of deformed hands, feet and faces.

The aims and methods of pre- and post-operative physiotherapeutic management are briefly stated. After corrective surgery, oedema or infection in a limb can nullify a good result. The management of these complications is set out. Though the metacarpo-phalangeal joints are not commonly affected in leprosy, when they do present with established contractures, mobilization poses a problem. To overcome this, metacarpo-phalangeal capsulotomy is performed. Following this operation, a new simple hook device with elastic traction has been adopted with success.

After tendon transfer, adhesions may develop. The methods used for breaking down adhesions, especially by various re-education techniques, are presented.

The success of pre- and post-operative physiotherapy greatly depends upon the selection of patients. One of the factors that makes the operation of tendon transfer or grafts unsuccessful is the stretching of the tendons; new techniques are suggested to prevent this stretching.

The aim stressed in this paper is a total rehabilitation of patients to a life of dignity and self-respect.

V 59

The care of the foot in leprosy

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The care of the foot in leprosy requires a team approach, making use of the skills possessed by physiotherapists, health educators, orthopaedic boot makers and surgeons. It is not necessary to have fully qualified personnel in each of these categories, provided that the skills presented by them are possessed by the individuals doing this work.

It is essential for those responsible for foot care to establish a rational scale of priorities. The following scale is suggested.

1. Identification of the patients whose feet are at risk.
2. Provision of health education in foot care, and arrangements for regular examination of the feet of those cases whose feet are at risk.
3. Provision of footwear.
4. Treatment of minor plantar wounds.
5. Treatment of major ulceration.
6. Surgical correction of deformity by simple methods.
7. Surgical correction of deformity by tendon transplantation and arthrodeses.
8. Amputation and provision of prostheses.

It is not possible to follow such a programme rigidly because patients will present who will

require immediate care because of gross ulceration and complications; but priority should be given to preventive care and health education.

Methods of foot assessment and examination and of health education will be described in detail. An account will be given of the principles to be followed in the design and prescription of footwear, and some recommendations will be made concerning the use of surgery as a means of preventing further ulceration in deformed feet.

V 60

The role of physiotherapy in the prevention of deformity and correction of early deformity

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Peripheral nerve lesions and lepra reaction are discussed as causes of primary deformity in leprosy. The value of physiotherapy in their treatment is stated. Muscle testing for the detection of the milder forms of neuritis and for the guidance of treatment of neuritis, is emphasised; also splinting and exercise given during reaction.

Anaethesia, paralysis and skin dryness are considered as predisposing factors of secondary deformity. The following measures are discussed for their prevention or alleviation:

Anaesthesia – education in daily care for affected limbs; choice of work; tool and shoe adaptation.

Paralysis – exercises and splinting.

Skin dryness – soaking, paring of callus and oiling.

Lastly, priorities in physiotherapy measures are outlined, and their adaptation for differing working conditions

V 61

Hydrotherapy as a method of treatment for contracted fingers

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Flexion contractures in leprosy are of several types; they include skin contractures, capsule contractures and contractures due to deep scarring. The skin contracture is the one most amenable to treatment. However, treatment with wax and oil and splintage is long and slow. The use of water in softening the keratin layer was proposed by Miss Kapiau. A group of patients with contracture of various types was selected for study of this therapy. The method was standardised and the results are presented in this paper. It is concluded that particularly for skin contractures hydrotherapy is of definite value for the treatment of flexion contractures of the fingers.

V 62

Patterns of deformity and their physiotherapeutic management in the reactive phases of leprosy

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This paper is based on a study of the mechanism of deformity in the upper and lower extremities of 50 patients in the reactive phases of leprosy.

Specific involvement due to erythema nodosum leprosum, panniculitis, myositis, lymphadenitis and oedema are described. Damage to nerves, joints, muscles, tendons and bones is analysed in 50 patients in reactive phases of leprosy. The etiology and progression of the various deformities resulting from such involvement is described. The mechanism leading to the production of deformity due to damage to the tissues is explained, and the resulting functional disabilities outlined.

The rationale of physical therapy during the acute and chronic phases is presented. Details of management used during the acute phase to prevent or minimise deformity are described. Techniques used to obtain improvement in the range of movement in affected joints and function of the limb as a whole during the quiescent phase is presented. Specific physiotherapeutic methods used in the management of complications such as oedema, neuritis, necrotising erythema nodosum leprosum and panniculitis are recorded.

The authors' experience with such methods of physiotherapy used in a large number of patients, is critically evaluated, and possible lines of future study and management are discussed.

EXPERIMENTAL LEPROSY – PATHOLOGY, WITH SPECIAL REFERENCE TO NEUROLOGICAL ASPECTS

VI 63

Behaviour of *M. leprae* in organized nerve tissue cultures

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Organotypic cultures of dorsal root ganglia, spinal-cord ganglia and whole cross sections (muscle somite, cord and ganglia) were prepared from rat fetal tissue using the technique of Dr. M. R. Murray and her colleagues.

Duplicate cultures of all three types were inoculated with *M. leprae* and *M. lepraemurium*, and compared with control (uninfected) cultures during an incubation period of 50 days. There was no evidence of a toxic reaction to the bacilli. The cultures continued to differentiate and establish the cellular inter-relationships found *in vivo*. Myelin sheaths formed *de novo*, and there was no breakdown of myelin sheaths once established. The muscle fibres became striated and their activity progressed from a sporadic fibrillation to a more organized contraction, which has been shown by G. Veneroni (personal communication) to be indicative of the formation of neuromuscular junctions *in vitro*.

The initial experiments which were designed to investigate the validity of using this experimental model system to study the affinity of *M. leprae* for the peripheral nervous system have been controlled by the inoculation of duplicate cultures with *M. lepraemurium*, which affects connective and reticulo-endothelial tissue; and by the comparison of tissue of peripheral and central nervous system origin.

The results of the distribution of acid-fast bacilli, as assessed by light and electron microscopy, will be reported.

VI 64

Experimental leprosy in mice

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An account will be given of the histological findings in normal and immunological crippled mice following inoculation of bacilli from untreated patients with lepromatous leprosy.

Among other things, it will be shown that lesions can be induced in mice which are in every respect comparable with those in the various well-recognized clinical forms of the disease.

VI 65

Ultrastructural process of cutaneous nerve alterations in leprosy

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Cutaneous nerve alterations in both lepromatous and tuberculoid lesions were compared with cutaneous nerve changes induced experimentally in mice under various conditions. Nerve degeneration caused by mechanical injury is characterized by myelin disintegration, axon degeneration, macrophage infiltration into nerve bundles and disruption followed by proliferation of perineural cells. The rapidly growing granulomas induced by injections of either complete Freund's adjuvant to non-sensitized animals, or by heat-killed mycobacteria to animals hypersensitized with the same mycobacteria, provoked a degenerative process similar to that of mechanically injured nerves. Demyelination, which occurs without any granulomatous response in animals hypersensitized with mycobacteria, is characterized by segmentation of myelin sheaths without any

remarkable axon degeneration, macrophage infiltration, or perineural alteration. Since the ultrastructural characteristics of cutaneous nerve changes in tuberculoid lesions resemble those induced by rapidly growing granulomas, we assume that the hypersensitive state which causes rapid granulomatous response to leprosy bacilli is responsible for cutaneous nerve damages in tuberculoid leprosy, as a result of mechanical pressure. Slight cutaneous nerve alterations in lepromatous lesions may be explained by the fact that the development of cellular infiltration is too slow to produce intense mechanical pressure resulting in nerve damage.

VI 66

Neurologic and cutaneous lesions produced in rats inoculated with isolates from human leprosy

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This report includes the development of neurologic and cutaneous lesions in rats inoculated at birth with (a) a *rat-passed* strain originally derived from the blood culture of a leprosy patient, and (b) an isolate more recently grown from a human lepromatous nodule. Both isolates were grown in transferable cultures in cell-free media.

Peripheral nerve involvement was found in histologic sections, and acid-fast organisms were seen in the Schwann cells and in nerve fibres. Foamy cells and acid-fast organisms were found in leproma-like lesions of the foot. Other granulomatous lesions appeared in the eye and facial areas.

VI 67

Cutaneous micro-circulation in lesions of lepromatous leprosy

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The micro-circulation of the cutaneous lesions of lepromatous leprosy was studied, using the Gomori technique of alkaline phosphatase. Three aspects were distinguished, corresponding to the phases of clinic evolution:

Early lesions, clinically discrete – the cellular infiltration forms sheaths around the dermal vessels, these being in small number.

Advanced lesions, nodular (lepromas) – the granuloma is at the centre of very ramified vessels; no impregnated vessels were seen outside the granuloma, nor were any granulomas seen without vessels.

Lesions in regressions – first there is a reduction in the number of vessels, the re-absorption of the granuloma starting only later. In the residual lesions, there is a vascular network comparable to that of the initial lesions.

Conclusions

1. The granuloma of the lepromatous cutaneous lesions intimately accompanies the vascularisation of the dermis, the latter increasing with the growth of the former. The regression of the granuloma seems to come about after the reduction in the number of vessels.

2. The known affinity of the lepromatous granuloma for cutaneous annexa is probably related to the vascular plexuses that surround them.

3. The absence of granuloma in Unna's layer can be explained by the absence of vessels in that area.

VI 68

Microradiography and fluorescent microscopy in the study of bone remodelling in leprosy

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In the study of bone remodelling in leprosy, new possibilities are offered by means of microradiography and fluorescent labelling *in vivo*. As a first report, the authors present observations still incomplete about bones of the leprous foot, with illustrations of osseous resorption and osteogenesis. They suggest a probable correlation between the two phenomena in special cases, but cannot yet offer an explanation.

VI 69

Sensitivity testing as a means of differentiating the various forms of leprosy found in Nigeria

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Sixteen selected leprosy patients were studied clinically and pathologically; in every case, the sensitivity of both affected and unaffected skin was compared with the sensitivity of a comparable skin area in a healthy Nigerian subject. A quantitative test was devised that could be used easily in the field. Six nylon threads of graded thickness were each applied three times in a random order but in a standard fashion to twenty-four lightly shaved skin areas in twenty-seven healthy Nigerians. In each area, the normal response-stimulus ratio was recorded.

In both borderline and tuberculoid leprosy, in which the lepromin test was positive, the response-stimulus ratio of unaffected skin lay within normal limits. In borderline and early lepromatous leprosy, in which the lepromin test was negative, the response-stimulus ratio of the unaffected skin was higher than in the normal series. In diffuse lepromatous leprosy the response-stimulus ratio was increased all over the body.

Alterations in skin sensitivity as demonstrated by this test could be a useful guide in the diagnosis of the various forms of leprosy, and could be of particular value when other methods of investigation are not available.

VI 70

The transmission of *M. leprae* to animals. Attempts to find an experimental model

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During a period of 12 years, the author has made a series of experiments in more than a dozen species of animals for the purpose of trying to find an animal naturally susceptible to infection by the leprosy bacillus. Using nerve invasion as a criterion for infection, infection has been obtained in several species of rodents. Of special interest have been infections obtained in the *Mystromys albacaudatus*, a rodent native to South Africa that has a life span of approximately 5 years. In histopathologic studies in this animal, well-defined lesions of dermal nerves have been found in animals dying more than 4 years after inoculation. A progress report on results in larger animals, including chimpanzees, hogs and dogs, will be given.

VI 71

The rôle of histology in the study of leprosy

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The study of microscopic tissue changes in leprosy antedated by approximately a generation the discovery of *M. leprae* by C. Armauer Hansen. A review of the histopathology of leprosy suggests two distinct periods. The first began in 1847 with Daniellsen and Boeck's illustration of a section of a nodule, and continued into the 1920s to close with the descriptions of tuberculoid leprosy by Wade and Pineda. It was a period of observation and record, and was followed by a later phase in which histologic studies entered into modern classifications of types of leprosy. This has been an interpretive period, contributing importantly to modern concepts of the mechanisms of the disease. With the merging of histologic and clinical studies of leprosy, the importance of the reactive episodes and the implications of immunologic features have evolved.

VI 72

Electron microscope study of the band structure on the surface of leprosy bacillus and other mycobacteria

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Okada and Sato had already noticed the occasional presence of peculiar band structures

on the surface of the leprosy bacillus, but their real nature is not yet known. Recently, we have had a lepromatous patient who has rapidly growing lepromatous nodules in spite of anti-leprosy treatment. In this patient, almost all leprosy bacilli from new lesions showed distinct band structures.

This band structure is a narrow band of about 150 Å thickness which surrounds the bacillary body just like a bamboo joint. Usually, band structures can be seen in the middle and near the one end of the bacillary body. In thick bacilli with diameters of about 0·5 μ, two or three band structures are seen situated very close to each other.

Similar band structures were found also in other mycobacteria, such as murine leprosy bacillus, H37Ra, avian tubercle bacillus (Jucho strain) and ICRC bacillus.

As these band structures were found in actively growing bacilli either *in vivo* (leprosy bacillus and murine leprosy bacillus) or *in vitro* (cultivable mycobacteria), it seems that they are related to the cell division of mycobacteria, especially to the cross septum formation of the cell wall.

VI 73

Diagnostic histopathological characteristics of leprotic epithelioid cell granulomas of the skin

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M. leprae is the only bacillus known in human disease that primarily invades nerves. For the pathologist, the demonstration of acid-fast bacilli in nerves is conclusive evidence of leprosy. This distinct characteristic of leprosy is often difficult to recognize in the usual paucibacillary epithelioid cell granulomas of tuberculoid leprosy skin lesions. Provided biopsy specimens are taken from the margins of active skin lesions, systematic microscopic examination will enable the pathologist to identify leprotic epithelioid cell granulomas. The demonstration of the variety of leprotic epithelioid cell granulomas with respect to involvement of nerves and location of acid-fast bacilli is the main object of this paper.

VI 74

A preliminary report on the light microscopic and electron-microscopic study of hypopigmentation in leprosy

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Hypopigmentation is one of the earliest signs in leprosy. The pigment melanin is produced by the melanocytes in the epidermis. Hypopigmentation may be due to the decrease in the number of melanocytes, or a decrease in the production of melanin following underactivity or abnormality of the melanocyte.

In this paper the number and character of melanocyte population in a lesion as compared to the contralateral normal skin in 20 cases of leprosy is reported. The morphological changes seen in melanocytes under light microscopic and electron-microscopic examination is described.

It is found that there is a statistically significant reduction in the number of melanocytes in chronically active lesions as compared to the number in the normal skin on the contralateral side. There is also a decrease in the strength of dopa reaction of the melanocytes in the lesions. In electron-microscopic examination an obvious reduction in the number of mature melanosomes is seen. No abnormal melanosomes are found. Three tuberculoid lesions examined in the acute phase show a significant increase in the number of premelanosomes, though fully melanized melanosomes are very few.

VI 75

The histoid nodule – its diagnosis and possible rôle in the natural development of lepromatous and borderline leprosy as well as an indicator of the changes therein induced by sulfone therapy

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This study is based on the follow-up of 32 patients admitted to the Eversley Childs Sanatorium, who had lesions diagnosed clinically, histologically, and bacteriologically as histoid nodules.

Biopsies done on 431 other cases of leprosy served as controls.

The main findings include the following:

Clinical – 1. Many early histoid nodules are transitory.

2. Histoid lesions can usually be distinguished clinically from other nodular lesions of lepromatous leprosy. Also, many of them develop on apparently uninvolved skin, whereas leprotic (LL) nodules are always located on diffusely infiltrated lesions.

3. There is a difference in the manner in which individual histoid nodules and the concomitant disease itself develop among patients who relapse after sulfone therapy, as compared to recently treated (non-relapsed) patients. The presence of histoid lesions may have a different significance under these two conditions.

Histology – The histology of an early histoid nodule was found to be essentially as described by Wade. The characteristic features are the spindle-shaped histiocytes arranged in whorls, which ingest and permit progressive multiplication of *M. leprae*.

Microbiology – Another cardinal finding in the histoid nodule is the presence of bacilli which are measurably longer than *M. leprae* as ordinarily seen in stained preparations. The existence of these elongated bacilli in histoid nodules permits further studies focused on the invading organism factor in the host-parasite relationship in leprosy.

VI 76

The scientific solution of the problem of leprosy

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The author notes that the origin of leprosy is obscure, and that the causes of functional cardiovascular disease are also unknown. He compares 15 symptoms of the latter with those of leprosy, and finds some remarkable parallels.

He argues that *M. leprae* is not a specific organism etiologically connected with clinical leprosy, and asserts that leprosy is not a communicable disease.

LEPROSY CONTROL

VII 77

Effect of sulphone on prevalence of leprosy

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This study reports the findings from 4 leprosy control units of Gandhi Memorial Leprosy Foundation, India, of which three are in the north and one in the south. Total population of the 4 control units was 94,129 in 1955 and 111,476 in 1965. All patients were treated in out-patient department, and infectious patients were not isolated.

The reduction in prevalence of leprosy in different units was as follows: Unit S from 15·62 to 10·50 per 1,000 (33%); Unit K from 27·63 to 7·60 (72%); Unit G from 10·48 to 4·54 (57%); and Unit M from 17·78 to 17·5 (60%).

In this study, the quantum of infection in the community was judged only on basis of bacteriologically positive lepromatous patients. The reduction in prevalence of bacteriologically positive lepromatous cases was as follows: Units S from 1·37 to 0·79, i.e. 42·3%; Unit K from 2·74 to 0·66, i.e. 75·9%; Unit G from 1·31 to 0·48, i.e. 63·4%; Unit M from 1·36 to 0·40, i.e. 70·6%.

It is concluded that even if infectious patients are *not* segregated, prevalence of leprosy can be brought down by treating them with sulfone in outpatient department. It should, however, be noted that this decline in prevalence is slow.

VII 78

The organization and methods of the leprosy control programme in Burma (1958–1968)

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WHO Consultant, Burma

The Leprosy Control Programme in Burma started in 1958 and is assisted by UNICEF, WHO and received also financial assistance from three International Voluntary Organizations. Three project areas were opened in 1958, and by January, 1968, there were 171,000 patients receiving treatment in 34 project areas covering about three quarters of the country.

The methods and logistics of the project are described in detail as well as the costs of the campaign calculated per patient per year both for in- and out-patients. Tables and maps illustrate the progress of the campaign. Prevalences as well as age distribution of the cases are given. The value of school and house-to-house surveys as case-finding methods is discussed.

VII 79

Strength and weakness of leprosy campaigns

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Abstract not received.

VII 80

Leprosy (including administration) in the Territory of Papua and New Guinea

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This paper describes the extent and nature of the leprosy problem as it exists today in the Territory of Papua and New Guinea, and the Administration's approach regarding its management and control.

The health department, assisted by Mission Health Services and in particular those services especially devoted to the management of leprosy, is committed to the policy of a public health approach to the treatment of leprosy with the general health services.

An average prevalence of 7·1 per thousand of the population emphasizes the need for a consistent and vigilant supervision of treatment and the regular examination of the community, especially contacts, for the detection of new cases, and follow-up of those already under treatment.

The natural difficulties of terrain, climate and transport are augmented by the difficulty of existent or developing services to keep pace with the rapid advances now being made in the country in all directions.

Problems of absenteeism and interruption of treatment due to complications of therapy, are further complicated by the emerging problem of altered attitudes to the traditional concepts of the disease on the part of educated and sophisticated members of the community.

Stress is laid on the need for a more compact exploration of the problem of leprosy, by a combination of all disciplines. In particular, epidemiological and therapeutic measures could be more profitably studied with the help of medical and social anthropologists in order to exploit local beliefs, ideas and attitudes regarding leprosy.

Finally, the role of established leprosy colonies is reviewed in the light of their future contribution to the control and management of the disease.

VII 81

Integration of leprosy control in health centre programmes

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Three significant developments make the expansion of leprosy control possible: the introduction of sulfones; the importance given to outpatient treatment in combating leprosy; and the integration of leprosy control activities into the basic health centre scheme.

Special efforts should be made to harmonize general planning with the developments in the expansion of rural health services and the integration of the specialised services, such as leprosy control, into the scheme of general health services. It is indispensable to balance the planned expansion of the health services with the financial potential of the country and its capacity for training public health personnel.

VII 82

"Lepra" project in Malawi

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A new project in Malawi (Central Africa) to demonstrate the possibility of removing all active leprosy from a limited area. The area selected is 2–3,000 square miles, and has a population of about 1 million. Communications are adequate for most of the year.

The leprosy prevalence is 15–20 per thousand. Patients hitherto were largely untreated or had received sporadic and inadequate treatment from a few fixed centres. One leprosarium exists in the extreme south-west corner of the area. Climate and terrain are described.

Preliminary planning began in 1965, but the project became operational in January, 1966, when the first three Malawian Medical Assistants joined the expatriate staff for training.

Because of the small numbers of experienced staff, mobile treatment units were introduced, first as a collecting point for patients, while additional staff could be trained for case-finding. Four mobile units are now established, 7,000 cases recorded and a 65% attendance achieved; these are under Malawian staff.

Case-finding has proved time-consuming in view of the results achieved. The various methods used and the difficulties encountered are described.

A centre was built in the grounds of the main hospital in Blantyre – an innovation in itself – where all adjuvant services are available as well as 36 acute beds. The outpatient work is controlled from here.

The types of leprosy so far discovered and the type and frequency of complications are described. Planning and costs for the future evolution of the project are discussed.

VII 83

Leprosy control in Ghana

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Primarily developed as a uni-purpose service, the Leprosy Service in Ghana is gradually being integrated into a common plan for control of the major communicable diseases. Ghana has a population of 7·5 million. The prevalence of leprosy is 1·1% and lepromatous type rate is 12%. The prevalence is higher in the northern half of the country than in the south. 20% of the total cases are children. Organised anti-leprosy work started in 1947, and the largest leprosarium (at Ankaful) was built in 1950. Initially, the work was limited to leprosaria and static clinics. Later, mobile treatment was organised, which extended all over the country by 1957. Laboratory control was developed in 1958, and training of para-medical workers has since been started. Improvements in institutional treatment were achieved by introducing corrective surgery, physiotherapy and occupational therapy. In 1963, case detection was started in pilot project areas. In 1967, administrative changes have made possible the bringing together of the various disease control groups, under one set-up and at regional levels; *epidemiologists have been appointed to integrate all communicable disease control programmes.* It is hoped that Rural Health Posts and Centres will gradually organize the routine leprosy treatment and follow-up examinations of patients, leaving the personnel of the Leprosy Service to break new ground.

VII 84

A leprosy service in a general hospital

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In 1960 a leprosy clinic was instituted at the PHS Hospital in San Francisco, and elevated to a leprosy service in 1966. This service is responsible for the operation of the clinic, the care of inpatients suffering from leprosy, the co-ordination of the various consultative services, the organization of the numerous teaching assignments, and works in close co-operation with the research service. It acts not only as a diagnostic and treatment centre, but is responsible for institution of prophylactic measures in family contacts of active cases of lepromatous leprosy, while they are admitted for institution of treatment.

The advantages of such a service integrated into a general hospital will be discussed, a report on its operation given, and its importance not only for patient and physician, but for the community stressed.

VII 85

Pogiri leprosy control project – methodology and achievements

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Pogiri, India

In 1962 a leprosy control project was started in Pogiri, India, by the Danish Save the Children Organisation, with technical assistance from WHO. The area covered is 5000 Km^2 with

a population of 1½ million. At present 28,732 patients within the area are under treatment.

The basic working unit consists of a field clinic held by a leprosy auxiliary worker who is responsible for case finding and case holding in a population of about 20,000. There are 70 such clinics spread over the area, which is divided into 5 zones, in each of which there are 10 to 15 clinics, supervised by 2 to 3 senior staff members. At headquarters, a small hospital provides facilities for hospitalization of patients in acute phases.

It has been proved by mass survey of a pilot area that 81 % of the existing cases were detected by health education, school survey and contact survey.

Through intensive supervision and personal contact of the worker with patients and the general population, an average attendance rate of 78 % has been achieved.

After 6 years of work, a regular decrease in the number of newly detected cases is observed. 8,083 patients have become quiescent, and treatment could be stopped in 2,783 patients who were declared "Released from Control". As a result the total number of patients under treatment has declined.

VII 86

Leprosy control and its associated problems in the highlands region of Territory of Papua and New Guinea

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In this paper the author discusses the functions and problems of establishing effective leprosy control in the semi-primitive New Guinea Highlands. The diversity of physical types and linguistic groups among the 860,000 people of this area, the inconveniences apparent by adverse climatic conditions for much of the year and by the rugged terrain, make the location and treatment of cases difficult.

In communities still basically existing on magico-religious beliefs and primitive ways of life as well as being scattered over an area of 23,000 sq. miles, the need for leprosy and general health education becomes strikingly imperative. The fact that many of the personnel called upon to aid in this programme are only semi-skilled in leprosy work and often not permanently domiciled, add to the difficulties of an overall control.

An average prevalence rate of 10 per thousand population requires consistent and continuous supervision of treatments at domiciliary level, regular patrolling of outlying areas to examine new or suspected cases and to review contacts.

The emergence of sophisticated patients poses a new challenge in social problems hitherto not encountered.

The goal is an efficient service designed to cover the area adequately and keep a close surveillance on every aspect of the disease.

VII 87

Portugal on the way to eradicating leprosy

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Leprosy was already reaching the endemic stage in Portuguese territory long before Portugal became an independent nation.

At the end of the Middle Ages, there were some 70 leprosaria in Portugal.

In the XVI century the disease was no longer endemic.

In the XVIII century, the entry into Portugal of sufferers from our overseas territories and other countries, among other factors, brought about the return of the disease.

In 1938 the public authorities launched the effective basis for the fight against leprosy, and the Rovisco Pais Hospital was opened on October 1st, 1947.

Based on the introduced legislation, registration of the sufferers was made, and completed in 1952. The total number of patients was 1,889, of whom 1,200 were in hospital.

In accordance with the legilsation, and in respect of "open" leprosy, we have admitted to hospital only those patients whose home conditions are unsatisfactory. For the "closed" forms, the problem does not arise.

At present, 9 wards of the 17 are closed. The hospital population is reduced to 500 patients, of whom more than half remain for social reasons.

VII 88

Leprosy in western Kenya

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The area covered included the Abaluhya, Luo, Kisii and Teso tribes, who prior to 1963 were in the Nyanza Province. Apart from the Luos the other ethnic group lived in scattered homesteads.

Because little clothing was worn in the past, it was easy for people to detect the disease; consequently, there was a strict code of conduct between patients and non-patients, with little or no contact. The situation has, however, changed recently owing to social innovation. This may have led to a spread of leprosy since the present generation, not only cannot recognise the disease, but try to escape detection by medical workers. The East African Community is striving to combat the spread of leprosy, by establishing clinics and training more leprosy workers, and making Medical Officers more aware of the disease. The scheme is based on that initiated by J. A. Kinnear Brown in Eastern Nigeria and Uganda.

The present scheme is costly, and a suggested alternative is the establishment of treatment clinics and homes in the villages supervised by leprosy workers. The patients could be accommodated in such homes at night, and thus continue their daily routine, whilst undergoing treatment.

VII 89

House-to-house surveys in the leprosy control programme (Burma)

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Between 1963 and 1965 as part of the Burma Leprosy Control Programme, house-to-house surveys were carried out in the hyperendemic belt around Mandalay in three districts (Mandalay, Kyaukse and Sagaing). Out of a total population of 220,246 persons, 208,081 or 94% were examined and 6,692 cases of leprosy were detected among them, (prevalence 32 per thousand). Sex and age were recorded and cases were classified as indeterminate, tuberculoid or lepromatous. The methods used in the surveys are described in detail and the epidemiological implications of the figures discussed. The importance of such surveys in areas of very high endemicity is stressed. Tables and maps will be attached.

VII 90

Leprosy and the general practitioner

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In countries where leprosy is prevalent, the general practitioner is the doctor to detect early cases and undertake their treatment. Leprosy should be treated by the general practitioner just as he treats other diseases, since it is only slightly contagious. Leprosy is an unpredictable disease with diverse manifestations, and the general practitioner has a greater chance than others to observe and record its clinical features and plan early effective treatment – thus preventing its complications.

The general practitioner should suspect leprosy in the case of doubtful macules in children, since no history of contact may be forthcoming, and anaesthesia is difficult to elicit in children. Early treatment with small doses of D.D.S. should be given in such cases. D.D.S. in small does is not teratogenic, and hence treatment should be continued throughout pregnancy. Small doses of D.D.S. twice weekly should be given to all persons in household contacts, irrespective of their ages, since all types of leprosy are infectious and D.D.S. has a definite prophylactic value.

VII 91

The rôle of institutional care in leprosy today – a new system of leprosy admissions

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Historically, the approach to the leprosy problem has been to isolate its victims from society. The earlier accepted norm of isolation has now become an anathema in medical circles. International, government and mission agency

funds in recent years have been increasingly directed toward non-institutional care and survey studies in leprosy. The exclusion of institutional care in favour of home care and treatment creates a new set of problems which must be recognised and dealt with. These problems are described, and the present conversion of a 55 year-old leprosy colony to the rôle of a leprosy centre is discussed. The complete answer then would seem to lie neither in the old system of long-term colonization or in the other extreme of out-patient-only care. Emphasis is placed on a programme of total care for short-term admission of problem cases.

IMMUNOLOGY, WITH SPECIAL REFERENCE TO HYPERSENSITIVITY IN LEPROSY

VIII 92

Impairment of phytohemagglutinin (PHA) and antigen-induced DNA synthesis in leukocytes cultured from patients with leprosy

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Cultures of peripheral blood leukocytes from 16 patients with lepromatous and 12 with tuberculoid leprosy were exposed to PHA, streptolysin O (SLO) and PPD. Duplicate sets of washed leukocytes plus these agents were grown for 7 days in media containing either 20% autologous or normal homologous plasma. DNA synthesis was measured by ^{3}H-thymidine uptake. With either medium, lepromatous leukocytes exposed to PHA showed no difference in DNA synthesis. This was less than in normal leukocytes exposed to PHA ($p > 0.05$). Synthesis of DNA by lepromatous leukocytes after SLO was significantly depressed in autologous medium ($p > 0.05$) but was normal in homologous medium. Responses of tuberculoid leukocytes to PHA and SLO were normal in both media. DNA synthesis after PPD by lepromatous leukocytes was greater in homologous than in autologous medium but not significantly so. The response of lepromatous and tuberculoid leukocytes to PPD was low when compared with leukocytes from normal tuberculin positive donors.

Plasma from some patients partially blocked responses of normal leukocytes to SLO and PPD but not to PHA. Studies with SLO indicate that blocking is independent of complement activity, ASO titer or concentrations of diamino-diphenylsulfone in plasma. Thus, both cellular and humoral factors may be operative in the depressed immune response of leukocytes cultured from patients with leprosy.

The results of skin tests performed on leukocyte donors and their correlation with *in vitro* studies will be presented.

VIII 93

Nature of the negative Mitsuda reaction in lepromatous leprosy

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Some knowledge of the nature of the anergy in lepromatous leprosy is essential for an understanding of the marked clinical and other differences between the tuberculoid and lepromatous forms of the disease. Studies are reviewed, mostly conducted in Cebu, showing that lepromin negativity in lepromatous leprosy is associated with a generalized impairment of delayed type hypersensitivity, as shown by the partial suppression of reactivity to tuberculin, *Candida albicans* antigen and other antigens in lepromatous patients as compared to tuberculoid patients and healthy controls. Other observations are included that tend to show that lepromin negativity results from the lepromatous condition rather than antedating and predisposing to it.

VIII 94

Delayed cutaneous sensitivity in lepromatous leprosy – response to transfer of leucocytes from sensitive donors

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We recently demonstrated that the lymphocytes found in lepromatous leprosy (LL) show a change in their capacity for blastic transformation in phytohaemagglutinin cultures. Many studies have shown that LL is accompanied by immunological changes.

The present study involved 13 leprosy patients who had been found to be anergic to the Fernandez reaction, tuberculin and histoplasmin. In accordance with the method described by Chase and Lawrence (1959), they

received injections of leucocytes from senstive donors, the authors themselves acting as controls.

A positive reaction to tuberculin was obtained in 3 cases, and to lepromin in 4 cases; both reactions became positive in 1 case. A total of 8 patients showed positive reactions out of 13 patients who had previously been negative and had received transferred leucocytes. No positive reaction was obtained for histoplasmin. The clinical condition, haemograms and proteinograms did not explain the variety of results obtained (5 patients remained anergic and 8 became positive).

It was shown that it is possible to modify – although only partially – states of delayed cutaneous immunity by means of lymphocyte transfer to patients with LL.

VIII 95

Histokinetic phenomenon

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A Histokinetic Phenomenon is one in which the animal organism when receiving an extrinsic and unspecific stimulus in its reticulo-endothelial system, responds with a predetermined histopathological process, depending on its intrinsic genetic state. The principles governing this phenomenon also govern the pathogenesis of leprosy and other granulomatous diseases.

The author based this conception starting from the fundamental discovery of the late lepromin reaction and from the observation of similar reactions in leishmaniasis, sporotrichosis and cutaneous tuberculosis – all of the tuberculoid type. It was also based on the verification of lymphohistiocytosis granuloma at the site of lepromin reactions classed as *negative*, and in the checking of the isopathic phenomenon.

His personal researches demonstrate that the stimulation of the reticulo-endothelial system, both in the healthy and the sick human being, through non-specific injections, may bring about two different types of response: tuberculoid or hyperergic, lympho-histiocytic or hypoergic.

In the healthy individual, this response indicates the immunological character of the granulomatous diseases from which he may suffer in the future; in those already infected, the response reproduces the granulomatous process of the actual disease.

VIII 96

Immuno-electrophoresis in the different clinical forms of leprosy

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Results of investigations by immuno-electrophoresis relating to the different clinical forms of leprosy are explained.

VIII 97

Immunologic analysis of *M. leprae* antigens and human sera by means of diffusion-in-gel methods

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Precipitating antibodies against two mycobacterial antigens, designated β and δ, have been demonstrated in sera from leprosy patients. The distribution pattern according to the types of leprosy, of the two antibodies, has been confirmed. Information is presented regarding the occurrence of the anti-β antibody in relation to the bacillary status of the patients. On the basis of the results obtained, it has been postulated that the two antigenic factors, β and δ, must form a part of the antigenic mosaic of *M. leprae*. A *M. leprae*-anti-*M. leprae* system has been established using mechanically disrupted bacilli separated from lepromas. Comparative immuno-diffusion studies have indicated the presence of one of the mycobacterial antigens in this system.

The study includes analysis of over two hundred sera, comprising one group of test sera and four groups of control sera. Sera from tuberculosis patients, patients with syphilis, from contacts of leprosy patients and from normal healthy individuals form the four control groups.

It has also been possible to obtain the related antigens in an isolated form by the use of Sephadex gels.

VIII 98

A study of the cross-sensitization between *M. leprae* and atypical mycobacteria using the Schultz-Dale method

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The writers used the Schultz-Dale technique for the study of possible immunological relations between *M. leprae* and various atypical mycobacteria.

Sensitization of the guinea-pigs was achieved by simultaneous peritoneal, subcutaneous and intradermal inoculation of suspensions of leproma which were rich in acid-resistant bacilli.

Mycobacterial antigens were used as a means of releasing the cultures which were developed in synthetic media, as well as purified protein derivatives (PPD).

The writers discuss the results obtained and the possibility of using them in leprosy research.

VIII 99

Antigenic relation and serological diagnosis in leprosy with fluorescent antibody technique derived from *M. lepraemurium*

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Fluorescent antibody techniques reveal an antigenic relation between *M. leprae* and *M. lepraemurium*. as well as between *M. leprae* and *M. Calmette-Guérin*. There are thus cross reactions between lepromatous rat sera and *M. leprae*, and between hansenian sera and *M. lepraemurium*. It has been possible to develop a serological method for the detection and titration of circulating antibodies in human leprosy, using Stefansky bacilli. The quantitative estimation of antibodies is measured by the progressive dilution of sera till they only just give an immunofluorescent reaction.

No antibodies can be found in normal healthy persons. Patients will all types of leprosy yield antibodies. The titre of antibodies varies with the clinical type of the disease. It is always high in untreated cases. It decreases with healing and effective treatment.

This technique is now in routine use, and over five hundred examinations have been made. It proves specially valuable in doubtful cases when clinical and histological findings are equivocal, and in patients with nerve damage only. Thus it was possible to discharge some patients in whom suspicion of leprosy was proved to be unfounded.

VIII 100

Cross reactivity of lepromin with other mycobacterial antigens

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Groups of guinea pigs were sensitized to purified lepromin or to *Mycobacterium kansasii*, BCG, *M. phlei*, *M. butyricum*, the Battey bacillus or *Candida albicans*, each emulsified in Freund's adjuvant.

Animals sensitized to the various mycobacteria reacted to the intradermal injection of lepromin with the formation of granulomas. This was a specific phenomenon, since there was no increased reaction to human dermis suspension, and only mycobacteria-sensitive animals reacted in this fashion.

Since these mycobacteria represent a wide spectrum within the genus, the results suggest that the positivity of the Mitsuda test in individuals free of contact with leprosy and of infection with *M. tuberculosis* may be due to exposure to any of a variety of mycobacteria that are widespread in nature.

Lepromin-sensitized animals did not show hypersensitivity to old tuberculin or purified protein derivative. These results suggest that lepromin-mycobacterial cross reactivity may involve antigenic determinants not present in "tuberculin". Such antigens may reside in the cell wall.

On the basis of the postulated relationship between positive lepromin reactivity and resistance to leprosy, these results suggest a possible correlation of mycobacterial ecology with the prevalence and clinical forms of leprosy.

VIII 101

Comparative experimental study of hypersensitivity to tuberoulin and lepromin in guinea-pigs previously inoculated with BCG by oral and intradermal routes

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BCG vaccination against tuberculosis has been performed by the oral route in some countries and by the intradermal route in others. In the prophylaxis of leprosy, BCG vaccination has been performed mainly by the oral route. Discussions continue concerning the immunological and practical advantages of one route over the other.

We tried to investigate that problem experimentally in guinea-pigs, as follows:

Material: 100 guinea-pigs, 3-4 months old, approximately 350 g. weight each, were used in this experiment. Vaccinations were made with either liophylized BCG or BCG Moreau (Rio de Janeiro) strain, maintained alternatively in glycerine-potato and bile-potato media.

Tuberculin hypersensitivity was tested with old tuberculin and purified protein derivative by the intradermal route. Lepromin hypersensitivity was tested with lepromin antigen (160,000,000 bacilli per ml.).

Technique: All the 100 guinea-pigs were negative to a previous tuberculin test. They were divided into 4 groups (A, B, C and D), with 25 guinea-pigs in each.

Group A – Control.

Group B – Intradermal inoculation with 0·05 mg of liophylized BCG.

Group C – Intradermal inoculation with 0·05 mg of BCG Moreau (Rio de Janeiro) strain.

Group D – Oral inoculation with 100 mg. of BCG Moreau (Rio de Janeiro) strain.

Thirty days afterwards, all guinea-pigs were tested with old tuberculin, PPD and lepromin by the intradermal route. The readings were made after 48 hours, 7, 14 and 21 days.

The results are discussed in this paper.

VIII 102

Passive transfer of lepromin sensitivity

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Inbred guinea pigs (strains II and XIII) were actively sensitized with a partially purified suspension of *M. leprae* which behaved in the same way as the usual lepromin when tested in human controls.

The animals became sensitized to the bacillary component of this lepromin; this was shown by the formation of granulomas corresponding clinically and histologically to those seen in positive Mitsuda tests in human beings, and by the lack of increased response to a suspension of normal human dermis prepared in the same fashion.

Mixed peritoneal exudate, spleen, and lymph node cells transmitted this sensitivity to isologous recipients.

Neither heat-killed cells nor pooled anti-mycobacterial serum nor serum from lepromin-sensitive animals could transmit this sensitivity.

These results indicate that the Mitsuda reaction is one of hypersensitivity directed towards the bacillary component of lepromin, and that it should be included in the category of delayed hypersensitivity states.

VIII 103

Lepromin test in non-contacts

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Material: Non-contacts: 330 persons 0–19 years old and 64 adults (62 over 40 years). Exposure to *M. leprae* not known.

Method: Lepromin with a bacillary content of 20 million bacilli/ml., provided by Instituto

Leprologia (Rio de Janeiro), was performed in 1962. Read at 48 and 72 hours, and weekly from 7th to 91st day. The larger response was taken into account. Reading criteria of early and late lepromin reaction: Tokyo Congress (1958).

Results:

1. Reading schedule for non-contacts: reported in Rio Congress, 1963.

2. Lepromin positivity (1+, 2+ and 3+) was 48% in age-group 1–4; 56% in 5–9; 87% in 10–14; 97% in 15–19 years; in people over 60 living in an asylum, 64%.

3. Lepromin positivity (1+, 2+ and 3+) in females (151); 57% and 77% respectively in age-groups 0–9 and 10–19. For males (179); 46% and 94% respectively. In males 10–19 years of age, the added proportion of 2+ and 3+ was higher.

4. Apparently results were similar in whites and non-whites 0–9 and 10–19 years of age.

5. The Fernandez reaction was positive in only one person (Mitsuda reaction 3+). Children 0–9 years old with negative or doubtful Fernandez reaction developed the Mitsuda reaction (1+, 2+ and 3+) in 45% and persons 10–19 years of age in 89%.

6. In the community of children studied, the percentage of tuberculin reactors is low while the proportion of lepromin reactors is high.

7. Almost 90% of 10–19 year age-group non-contacts with negative Mantoux (PPD I TU) had positive Mitsuda reaction. The number of tuberculin reactors was too small for a conclusion to be drawn. Apparently in Mantoux positive non-contacts, the proportion of Mitsuda positivity was slightly higher as well as the proportion of Mitsuda 2+ and 3+.

VIII 104

Diluted lepromin in the investigation of contacts of leprosy patients

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An initial investigation was performed in Venezuela by one of us with Drs. J. J. Arvelo and Luigi Molinengo. (Rev. de Sanidad y Asistencia Social 23, nos. 1 and 2, 1958).

Now, starting with a standard lepromin with 160,000,000 organisms per ml., we have continued to use a dilution of 1/400.

The results obtained, in %, for the Mitsuda standard and this prepared dilution, adjusted to the criterion of classification laid down, are as follows:

For reactions –

± 36·1 and 30·3% respectively
\+ 9·3 and 9·1% respectively
++ 54·1 and 52·7% respectively
+++ 5·9 and 1·9% respectively

We emphasize changes of the Mitsuda tests ± and + to ++ and +++ after application of BCG reinvestigated with the same dilutions.

Considering the proved harmlessness of BCG, that differences between the diluted reagents are barely apparent, and that all forms benefit from the stimulating power of BCG, we think that these dilutions are of application in the investigation of contacts, producing necrosis in strong reactors and a substantial saving of antigen in general.

Note: Studies have been performed in collaboration with State dermatologists and mobile teams of the Director General of Public Health, health control department: (Medical Director: Dr. A. Gimeno de Sande).

VIII 105

Reactions of the skin to lepromin and filtrates of normal skin

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Studies of lepromin and intradermal reactions have been carried out on children and adults. The results were analysed from the reactional and histological points of view.

RECONSTRUCTIVE SURGERY

IX 106

Restoration of function of triple nerve paralysis in the leprosy hand

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The most important functional aspect of the flexor mechanism in the hand is related to the synergic activity of the dorsiflexors of the wrist. The loss of extensor function of fingers and thumb in addition causes considerable disability when the radial nerve is paralysed. In leprosy, the deformity resulting from paralysis of the ulnar, median (low) and radial nerves is most crippling and disabling. The restoration of function in such a hand is always challenging.

During the 15 year period, 1951 to 1966, 2,424 hand operations were performed in the Department of Orthopaedics and Leprosy Reconstructive Surgery, Christian Medical College Hospital, Vellore, South India. Of these, 40 had total paralysis of the hand, i.e. paralysis of ulnar, median (low) and radial nerves. They had either tuberculoid or dimorphous leprosy.

The restoration of function comprised: mobilizing the joints of the fingers by physiotherapy, followed by staged surgical procedures. Wrist stabilization was followed by restoration of extension in fingers and thumb, and intrinsic and opponens replacement operations. The earlier cases had wrist fusion procedures for the stabilization of the wrist, whereas the recent cases had tendon transfer procedures only. The complications and long-term functional results of these various methods are compared. The period of follow-up for the operated patients ranges from 1 to 12 years. The operation techniques are also briefly described.

IX 107

Compression arthrodesis, by a new-type compression plate, in the treatment of Charcot's joint of the ankle in leprosy patients

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The treatment of Charcot's joint is one of the important problems in the orthopaedic field of leprosy, as it is in other diseases. Arthrodesis is well recognized as an effective surgical procedure for Charcot's joint. In particular, compression arthrodesis has been recommended as a good method, because by this procedure the fusion of the joint can be obtained more readily than by other methods.

Therefore, we have employed the method of compression arthrodesis by a new-type compression plate in the treatment of Charcot's joint of the ankle in leprosy patients. The new-type compression plate was adopted not only for internal fixation, but also as a compression device. This compression plate has been developed in our clinic, and needs no appliance to exert compression, because it has special characteristics in the groove of the screw of the plate. The groove has an inclined surface to draw together and to compress the bones to each other, when the screw is turned into the bone.

Fusion of the ankle joint can be obtained simply, easily and surely by this procedure.

IX 108

Patterns of nasal deformities

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This paper is based on a study of 1,880 patients with lepromatous leprosy. The detailed

anatomy of the external nose is outlined, and the importance of the lateral cartilages in maintaining normal contour is emphasized.

Damage may be caused to the bony components, consisting of the nasal bone, margins of the piriform fossa, the maxillary spine or the alveolar process. Other important factors are: destruction of the cartilage of the lateral wall, the septum or the alar; destruction of the mucous membrane lining the lateral wall of the septum or the floor, and of the subcutaneous tissue of the floor and the naso-labial angle. The damage may be caused by primary lepromatous granuloma, secondary necrosis or infection.

Apart from the collapsed "clover nose" in its various stages, other deformities occur, such as the withdrawing of the columella, the narrowing of the columellar-labial angle, the upward and backward shifting of the alar, columella or upper lip, the foreshortening of the nose, "beaking" and flattening of the nose, conditions that have not hitherto been described.

Each of these deformities results from a specific pattern of involvement of the various components of the external nose. These are described in detail, with illustrations, photographs and X-rays.

IX 109

The foot in leprosy

W. Felton Ross
Alert, Addis Ababa, Ethiopia

IX 110

An itinerant surgical service for leprosy patients

J. K. A. Clezy
Madang, New Guinea

Four years' experience in New Guinea has shown that the introduction of surgical services for leprosy patients has an invigorating effect on the whole programme.

Because of poor surface communications and scattered population, it has been impossible for a single institution to serve more than a fraction of patients. Decentralisation has been necessary, and the benefits derived from a surgeon visiting six or more hospitals greatly outweigh the disadvantages.

The success of this approach depends on adequate training of leprosy workers in basic physiotherapeutic techniques. This is practicable in a short time when carried out in a busy surgical unit.

Although the aim of each surgical operation is to improve function and assist the patient to preserve tissue, the place of surgery in the overall leprosy programme must always be kept in mind.

We have found that surgery forms a useful bridge between the leprosy department and the general medical services, both at graduate and undergraduate levels. This situation must be exploited to the full in order that more doctors may come to accept the care of leprosy patients as their business, instead of referring most of them to a thinly-spread leprosy department.

IX 111

Metatarsectomy for intractable plantar ulceration

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Surveys conducted on out-patients at the Acworth Leprosy Home and on in-patients at the Chembur Leprosy Beggars' Home, Bombay, have shown that recurrent plantar ulceration poses the biggest physical problem in the rehabilitation of leprosy patients.

While care of the feet and protective footwear can help to prevent damage to insensitive feet, once ulceration has occurred there is a great danger of recurrence. These ulcers – generally resulting from walking stress – are situated chiefly under the heads of the metatarsals and under the proximal phalanx of the great toe. Destruction of one metatarsal head results in shifting of stress and ulceration under the adjacent metatarsal head. Even with the use of rigid-sole footwear, it is difficult to prevent recurrent ulceration in the badly scarred foot.

Six cases were selected from the ulcer clinic of our department, representing nine feet with intractable recurrent plantar ulcers. Repeated previous attempts at healing by the use of plaster-of-Paris casts and rigid footwear had failed to prevent recurrence.

Resection of the head and distal half of the metatarsal bones was undertaken in these cases, and the patients followed up over a period of six to fifteen months. All but one of the ulcers

remained healed. The patient with the unhealed ulcer took to wearing a simple micro-cellular rubber sandal again.

The foot, though short, retains its general appearance (including the toes), and hence is acceptable to the patients.

The preliminary encouraging results justify further trial of this method in selected cases of persistent ulceration.

IX 112

Personal experience of surgical treatment of leprous paralyses and proposal of a therapeutic scheme

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The treatment of 125 cases of leprous paralysis of the intrinsic muscles of the fingers, 45 cases of paralysis of opposition of the thumb, and 25 cases of external popliteal paralysis carried out personally by the author, has given him the opportunity of using most of the accepted palliative surgical interventions. This experience enables him to compare the practical difficulties and the results of the various procedures: some of the results have been reviewed over 7 years later.

While most techniques give good results in good hands, a "mass surgery" programme in Africa by non-specialized surgeons requires simple and straightforward operative techniques which do not need long post-operative supervision or re-education, and which are not followed by post-operative complications. A therapeutic scheme is proposed:

Intrinsic paralysis of the fingers

Normal procedures

Fingers not stiff or slightly stiff – 2 last fingers – Zancolli's operation; 4 fingers – Zancolli's operation, or Brand's.

Fingers stiff (after physiotherapy) – Transplantation of one or two superficial flexor tendone.

Exceptional procedures

Fowler's tenodesis.

Proximal inter-phalangeal arthrodesis.

Paralysis of opposition of the thumb

Normal procedures

Thumb not stiff – Ney's operation, or better – transplantation on the long extensor of the thumb of the short extensor bent round the great palmar.

Thumb stiff (after physiotherapy, skin grafting, capsulotomies) – Thompson's operation, with fixture of the distal strip on the long extensor of the thumb.

Exceptional procedure

Tenodesis of extensor pollicis brevis on the cubital styloid of Brooks.

External popliteal sciatic paralysis

Carayon's operation.

IX 113

Surgical treatment of leg ulcers in leprosy

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The author considers that a standard type of grafting suitable for the treatment of leg ulcers in leprosy cannot be advocated. Various factors, general and local, indicate the most suitable skin covering for each case.

Following this advice, he uses dermo-epidermal autografting, fresh and preserved homograft, or the graft of total abrased skin and the dermal graft.

He offers a critical analysis of his experience, emphasizing the advantages of each method, and calls particular attention to three procedures that are in general use by surgeons dealing with patients suffering from leprosy.

IX 114

Recent trends in the reconstruction of the face in leprosy

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Depressed nose – Insertion of support to correct the depressed nose without providing lining is futile. Post-nasal inlay still remains the most simple and effective method of providing lining. The cantilever bone graft has been virtually replaced by the acrylic prosthesis.

The sagging face of leprosy allows the use of nasolabial flaps for lining. This method has the advantage of being one-staged, as it does not usually require the provision of additional support. It also provides a nasolabial face-lift.

Facial palsy – The temporalis sling remains an efficient method for the correction of lagophthalmos. Lower facial paralysis is best dealt with by transfer of the anterior half of the masseter muscle into the angle of the mouth, with or without a fascia lata extension. Intra-oral resection of the opposite muscle helps in achieving balance of facial features.

Eyebrows – The use of free full-thickness grafts from the scalp remains the procedure of choice for loss of eyebrows. Occasionally, a pedicle scalp flap or a temporal artery island flap may be utilised. Eyebrow prosthesis may be a substitute for surgery in certain cases.

Ears – The hypertrophied ear lobule can be trimmed by one of several recognised methods.

Helical irregularity is dealt with by trimming of helical cartilage or a Dufourmentel's procedure.

The nasolabial face-lift improves the cosmetic result, and plication of underlying muscles gives fulness to the sunken cheeks. The finer circumoral wrinkles can be removed by a chemical face-peeling.

IX 115

Cockett operation for reconstruction of the nose in leprosy patients

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The operation described is a development of Gillie's posterior nasal epithelial inlay. After freeing the nose from the underlying bone through a nasolabial sulcus incision, the upper part of the resulting cavity is filled with minute cartilage chips and the lower part with a skin graft bag stuffed with pledgets of cotton wool soaked in a 2% suspension of chloramphenicol in paraffin. After closing the incision in the nasolabial sulcus, a crest and columellar bone graft are inserted through the columellar incision. On about the 12th day, the skin graft bag is perforated through the nares, the packing is removed and the airway is restored.

IX 116

Orthopaedic surgery of the hand in Hansen's disease

J. O. BENIMELI

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From 1957 to 1968 we have carried out different orthopaedic procedures described for hands affected by Hansen's disease. At first we carried out Bunnell's technique, then Brand's, and Zancolli's; at present we use Gosse's.

This study will attempt to demonstrate the superiority of this last method which, while restoring the function of flexion of the metacarpal-phalangeal joints, avoids their hyperextension, and does not present the difficulties of previous techniques. This is to say: with Bunnell's technique we have observed, especially with lepromatous patients, difficulty in attaining perfect healing of the digital wounds.

With Brand's technique, in the white race, in which the hand is harder than in the black, there is lack of power in metacarpal-phalangeal flexion. We have had several cases of adhesions and fibrosis of the tenoplastia, and on occasions, digital stiffness: this last result we have also observed with some frequency with Bunnell's technique. Metacarpo-phalangeal hyperextension is avoided with Zancolli's method, but the mechanism of closure of the wrist is defective.

IX 117

Periapical granulomas and leprosy

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The author has studied 72 granulomata from leprosy patients of both sexes covering a wide range of ages and also the various types of leprosy. He removed and examined samples from all teeth: part being used for bacterioscopy and bacteriology, and part for histology and pathology. He found alcohol-acid-fast bacilli in 62·5%.

Tochihara and Murakami found *M. leprae* in the pulp of teeth in which there were no lesions: this could account for their destruction.

He concludes that leprosy can produce periapical granulomata through invasion of the pulp from the blood vessels; this leads to

destruction of the pulp by chronic reactions of low intensity, followed by infection or slight irritation of the periapical tissues. This, in turn, produces a proliferative and defensive reaction of the alveolar bone, as a result of irritation of the root canal.

IX 118

Deformity in Korean out-patients

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Over 1,000 out-patients in a leprosy programme in the Republic of Korea are classified according to the presence or absence of deformity on the first attendance. The majority of the patients come from rural areas. The classification of deformity is based on the W.H.O. scheme (1961).

Four-fifths showed evidence of deformity (including anaesthesia). Madarosis occurring in one-third was considered a misleading sign of lepromatous leprosy in Koreans, since it was seen in negative untreated patients and not in one-quarter of the positive lepromatous patients.

Lagophthalmos or facial paralysis was present in one in ten of all patients.

Anaesthesia (Grade 1) of one or both feet was present in one-third of the patients, and similarly the hands.

One-third of these patients had had no treatment previously and two-thirds of these already had deformity; half of them had only one site affected, usually the face (madarosis) or a limb (anaesthesia). A few patients even had all four sites involved where there had been severe polyneuritis or reaction before the beginning of treatment.

IX 119

Contributions to the histopathological investigation of the evolutionary process of laryngeal infiltrations in lepromatous patients

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The frequency of laryngitis in lepromatous patients does not extend to specific infiltration of the vocal cords.

Glottal infiltrations may develop beyond the epiglottis, over a long period of several years, on the anterior and posterior commissures, giving rise to laryngeal stenosis.

In patients who have undergone tracheostomy for laryngeal stenosis, studied for several years, the antero-posterior third of the vocal cords is found to be free of specific infiltration. The voice remains normal in spite of the persistence of lesions in both commissures which make it necessary to retain the tracheal cannula.

We can compare infiltrations of the antero-posterior commissures of the glottis with infiltrations of the labial commissures with their corresponding lesions.

Investigation of the larynx at autopsy has confirmed our findings in respect of infiltrations of the vocal cords.

IX 120

Surgical solutions of different problems in leprosy patients

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The authors offer a general account of their experience in more than 1,200 patients treated for different late sequelae of leprosy.

They offer some practical solutions, some being original, for the treatment of:

Pharyngeal stenosis
Fibrous stenosing laryngitis
Nasal deformities
Septal perforations
Stenosis of the narines
Entropion
Lagophthalmos
Deformities of the ear-lobes.

BCG AND PROPHYLAXIS

X 121

The trial of BCG vaccination against leprosy in Uganda

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This trial began in 1960. The participants were all children related to, or in contact with, leprosy patients (most patients being under treatment, and some having lepromatous leprosy). Children with leprosy on admission, or with strong tuberculin reactions, were observed without vaccination; the others were assigned alternately to a BCG-vaccinated and an unvaccinated control group, which were thus similar apart from vaccination. The main intake lasted two years, and newborn babies in trial families were added until 1964.

The 19,000 children are scattered in their families throughout a large district, with no towns or villages. Despite population movements, a high proportion have been seen at intervals and examined for leprosy, using methods which ensure that skin lesions are recorded without knowledge of the vaccination history. The current results indicate that BCG gives about 80% protection against early forms of leprosy in this part of Africa; it is too early to assess protection against lepromatous leprosy.

These early results are very encouraging, but personal experience in Africa since 1930 suggests that the pattern of leprosy is changing, perhaps partly as a result of chemotherapy. It would therefore be unwise to generalise from these results or to reach a premature conclusion.

X 122

BCG and prophylaxis – the Karimui trial

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This paper presents the results of 5 years' observation of a leprosy-endemic, tuberculosis-free and untreated population, approximately half of which was vaccinated with BCG, the remainder receiving saline (allocated at random). The incidence of leprosy in each group was measured by the detection of all new cases at serial surveys in 1964, 1966 and 1967. The clinical diagnosis of over 90% of all cases detected has been confirmed by histopathology. BCG vaccination causes a reduction in incidence in the age group 10–29 years, but after 30 years of age and under 10 years, no significant differences are noted.

The efficacy of BCG vaccination can be evaluated with precision only if two other factors are considered: (a) the degree of exposure to infection of the vaccinated and unvaccinated groups in relation to contact with the two polar types of leprosy; and (b) reactivity to human and avian tuberculins in both vaccinated and unvaccinated groups. The results of the Karimui trial to be presented will take both these factors into account.

X 123

BCG vaccination of children against leprosy – preliminary results of WHO trial in Burma

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The main *objective* of the research is to observe in a highly endemic area whether BCG vaccination protects against leprosy the child population (0–14 years) not exposed to *M. leprae* at home, but which might have been exposed to the bacilli elsewhere.

Material and method – The study is especially concerned with children whose tuberculin reaction measures less than 10 mm., but those with reaction measuring 10 mm. and over are also assigned to trial groups. Size of sample: 4,700 children, 1–14 years, not infected with

tubercle bacilli should be assigned to each trial group.

Tuberculin testing: 2 tuberculin units of the purified protein derivative No. RT23 in dilution with Tween 80. Reading after 48 hours in terms of *induration size* only. BCG vaccination is allocated independently of the result of the tuberculin testing. Children to be vaccinated are injected intradermally with 0·1 ml. of *freeze-dried* vaccine (Glaxo). Systematic assessment of post-vaccination allergy is performed in random samples of the study group. Viability of the *field vaccine* is checked occasionally.

It was considered important to allocate to both groups children belonging to the same family. Sex, and especially age, were then taken into consideration. Child population has been re-examined once yearly. Diagnosis and classification checked by three specialists.

Preliminary data and results – The trial started at the end of August 1964, in Singu township, Mandalay district. In October 1967, it was decided to extend it to Shwebo, Wetlet and Khin Oo townships. The preliminary data, up to the end of February 1968, are as follows:

	Registered	Examined
Total population	63,096	57,355
Below 15 years	28,205	27,229
15 years and over	34,891	30,126

Tuberculin reading (children): Less than 10 mm.: 20,092; 10 mm. and over: 2,897.

Children included in the trial: BCG group – 11,432; control group – 11,420.

Follow-up examination (overall coverage in the order of about 90%):

Annual follow-up	No. of children examined	No. of patients	Trial groups BCG	Control
1st	15,433	96	54	42
2nd	6,313	42	20	22
3rd	3,800	31	14	17
Total		169	88	81

In both groups, only the early forms of the disease – mainly tuberculoid – were seen.

Conclusion – Up to February 1968, the data do not seem to show any evidence that BCG vaccination decreases the incidence of leprosy or influences the form of the disease in the new cases. It is still premature to draw any definite conclusion from the data collected so far.

X 124

Chemoprophylaxis in leprosy

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The paper is based on a five-year study conducted in South India to discover if DDS has any prophylactic value against leprosy among child contacts exposed to infectious cases in their families. The number of contacts in the study was 718, half of whom received DDS in twice-weekly doses, and the other half received placebo tablets and served as control. The administration of tablets and follow-up of contacts was conducted by using the "double-blind" technique. "Treatment" was terminated in contacts whose index cases became bacteriologically negative and remained so for three years.

Sixty-seven cases of leprosy have occurred among the contacts, 46 among those in the control group, and 21 among those who received DDS. Statistically, the difference is highly significant, and shows an efficacy rate of about 55%. None of the cases detected was of lepromatous type; most were either tuberculoid or maculo-anaesthetic. Analysis of the findings by age, sex, duration of treatment, bacteriological state of index case, etc., shows some interesting features. The conclusion is that chemoprophylaxis with DDS is effective in preventing leprosy among child contacts exposed to infectious cases in their families.

X 124A

A methodological comparison of three trials of B.C.G. in leprosy

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X 125

Cell walls from BCG as vaccine against *M. leprae* in mice

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BCG, an anti-tuberculosis vaccine, provides protection against the foot pad infection in mice with *M. leprae*. Although ordinary preparations of BCG cell walls are not effective as vaccine against tubercle bacilli, oil-treated cell walls provide good protection against pulmonary infections of mice with *M. tuberculosis*. Similarly we have found that oil-treated BCG cell walls were effective as vaccines against *M. leprae* infections in mice. The amount of protection was about as great as that provided by intact (living) BCG, and was distinct, following either intradermal or intravenous administration. Cell walls that had not been treated with oil provided no protection. The amount of lymph node enlargement that followed intradermal vaccination was distinctly less with cell wall vaccines than with BCG.

X 126

Antileprous prophylaxis in countries of low endemicity

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In countries of low endemicity, microfoci of leprosy may call for control measures which vary according to the intensity of the problem; sometimes, these may mean examination and massive BCG vaccination of the whole population.

We emphasize the rôle of BCG in antileprosy prophylaxis in all situations. A single vaccination may not suffice to change the immunological state of the individual. If after the first BCG vaccination, the state of approximately 80% of the people changes, the remaining 20% (less developed immunologically) require more attention, since new cases of leprosy will appear in this group (with the exception of cases which declare themselves after the vaccination, the "post-BCG cases"). The revelation – as allergic leprosy patients – of a significant number of patients in the incubation stage is, we consider, one of the real benefits of the use of BCG in leprosy.

X 127

The programme for BCG vaccination in Los Angeles

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The contacts of over fifty families with leprosy were studied and vaccinated in a programme which began in December, 1966. Preliminary tuberculin tests were performed and either British vaccine or Rosenthal vaccine was used. Results and reactions were noted and compared for efficacy.

X 128

Chemoprophylaxis of leprosy contacts with DDS

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The effectiveness of DDS administration as a prophylactic measure to the children of leprosy patients and leprosy contacts is evaluated through two separate field experiments.

Experiment I – A total of 760 children, one of whose parents had leprosy, living at various preventoria throughout the nation, were divided into two groups, an experimental group of 325, and a control group of 435. DDS, in a dosage of 50 mg. to 300 mg. per week, was given to the children of experimental group.

Throughout the observation period of 2 to 7 years, only two of the children in the DDS-medicated group developed leprosy, while among the children of the control group 31 children (7·1%) out of 435 developed leprosy.

Experiment II – A total of 1,527 leprosy contacts were included in this study. The first group consisted of 778 household contacts from 156 bacteriologically positive leprosy patients, and the control group of 749 individuals were household contacts from 160 leprosy patients of various types in Kangwondo province.

Throughout the observation period of 3 to 10 years, one case of indeterminate leprosy was observed in the DDS-medicated group, while 13 cases of leprosy (1·7%) developed in the control group.

X 129

Observations on the prophylaxis of leprosy in the USSR by vaccination

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USSR

Of 131 children who had been born to patients suffering from leprosy over a period of 10 years and who had been vaccinated, only one was affected by the disease (T); of 230 non-vaccinated children 15 were affected (L-3); of 3,772 adults vaccinated, 3 were infected; whereas 13 of 2,662 non-vaccinated adults were (L-8). The results are valid.

In the region of Astrakhan, 2 of 2,230 vaccinated adults were affected (L-3); 21 of 13,622 non-vaccinated adults became infected (L-8). Similar results were obtained in the Republic of Kasakh. In the district of Rostov, of 3,511 subjects with a negative tuberculin reaction, 76% became positive after vaccination by mouth and 92·3% after subcutaneous vaccination.

There used to be an annual incidence of 17–23 new cases in the region of Asov; in the first two years after total vaccination, there were 9 cases, and not a single one has occurred after 1960.

CLINICAL AND SURGICAL ASPECTS OF NERVE DAMAGE IN HUMAN LEPROSY

XI 129A

Leprous neuritis of nerve trunks – clinical, operative and gross morphologic findings

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A five-year study on 27 subjects (22 arms and 5 legs) with polyneuritic form of leprosy, conducted over the last five years, is presented. The majority of these were tuberculoid, the remaining being dimorphous in type, mostly of long duration. Pre-operative sensory, motor and general clinical findings consistent with the type of leprosy were observed in each patient. The majority of patients volunteered for surgical treatment for relief of nerve pain. All of them showed thickening and/or firmness of the ulnar and/or median nerve in the arm and of the lateral popliteal and/or posterior tibial nerve in the leg.

An extensive operative exposure, extending from the mid-arm to the distal palmar crease, was used to study the ulnar and median nerves together with their branches and surroundings. Structures compressing these nerves such as deep fascia, fibro-osseous tunnels and adhesions were looked for, and extraneural release of the nerves was effected. The maximal thickening of the ulnar and median nerves was at the expected sites in the lower arm and forearm respectively. The detailed structure of the exposed nerves was examined under magnification. The nerve bundles were generally pale, fibrosed and difficult to identify and separate. Electrical stimulation of the nerves, their bundles and branches and muscles at operation usually confirmed the pre-operative clinical findings. Biopsies of bundles of nerves, trunks, subcutaneous nerves, muscles, fascia and skin were carried out. In 3 cases, with total sensory and motor paralysis of long duration, tótal excision biopsy of the ulnar and/or the median nerve was performed.

The leg exposure of the lateral popliteal nerve at the knee, its two terminal branches around the fibula, and of the posterior tibial at the ankle and of its terminal plantar branches in the foot, was carried out. Again, the expected sites of nerve compression, especially at the fibular neck and against the medial malleolus, were confirmed, the nerve stimulated electrically, and in 4 of the 5 cases, they were excised *in toto*.

No attempt was made to transpose or desheath the nerves, and their blood supply was carefully preserved. The majority of the patients experienced post-operative relief of pain.

XI 129B

Leprous neuritis of nerve trunks – pathology, pathogenesis and electromyógraphy

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Pre-operative electromyographic examination could be conducted only in 7 of the 25 nerve exploration studies on the arm and in all of the 5 explorations on the leg. Post-operative electromyographic evaluation was possible in about twice this number, and in some patients repeated examinations were possible. Electromyography proved a more sensitive indicator of denervation than did the motor nerve conduction velocity. The latter was not significantly reduced in some cases that had obvious clinical deficit. Consistent with the clinical and operative findings, there was no evidence of selective ulnar or median nerve damage in the wrist and hand, since all prolonged distal latencies were accompanied by markedly reduced elbow-wrist conduction velocities.

On histological examination, the more severely damaged nerves, either large trunks or outaneous or motor branches, often showed gross destruction and disorganisation by varying combinations of fibrotic and inflammatory changes. This happened irrespective of the type of leprosy, but the connective tissue increase was more irregular in tuberculoid

nerves. Schwann cell proliferation was more clearly recognisable in the lepromatous and dimorphous types of nerves. The rôle of the Schwann cells as the principle carrier of *M. leprae* was clearly manifest in all these cases, where the affected parts of the nerves were loaded with leprosy bacilli. The latter were seen elsewhere infrequently, such as in interfunicular histiocytes.

The nerves that could be totally excised at operation were found to be almost completely free from infection and from reaction. This is true of the median nerve from the middle of the forearm upwards and of the ulnar nerve from the middle of the arm upwards, even when at the wrist and at the elbow, respectively, these nerves were heavily bacillated and almost destroyed.

In all, 60 muscle biopsy specimens were examined. Multiple muscle "biopsies" from any one patient permitted comparisons of the varying grades of neurogenic atrophy observed.

Otherwise the histological details of this atrophy were identical with those described earlier (Dastur, 1956). Intramuscular neuritis was again observed, though infrequently, as in the earlier study, being detected now in 10 of the 60 muscles examined histologically. In 4 cases, AFB were detected in these muscle-nerve twigs, and in one instance in the intrafusal muscle fibres.

XI 130

Direct surgical treatment of the large nerve trunks in leprosy

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1. The *mechanism* of the neural impairment or hyperalgesia due to neuritis has been re-assessed by personal work in neuro-radiology (visual neurography, lymphography, selective arteriography of the main vessels) and confirmed by histology (R. CAMAIN).

2. The *choice of methods* has become adapted to the needs; simple débridement of the osteo-ligamentous tunnels, exoneurolysis, fascicular endoneurolysis as used by us since 1957. Their particular indications are studied.

3. The persistent ineffectiveness of medical and orthopaedic treatment justifies direct surgery, but a *strict selection* of cases is essential. This present study deals with 236 operated cases.

3.1 117 cases of hyperalgic neuritis, with 11 immediate failures, but 9 cures after recovery and 2 relapses.

3.2 39 cases of nerve defect seen early: 30% sensory-motor cures, 30% motor cures, 40% slight improvements and only 7% relapses.

3.3 Neuritis of the posterior tibial nerve with persistent plantar ulceration, but without bone lesions, or after cure of the bone lesions: 7 failures out of 46 neurolyses, or 14%.

3.4 Neuritis which had developed for about one year and showing partial impairment of function or a slowly progressing form, or a total clinical deficit with partial persistence of electrical conductivity. 5 failures out of 11.

3.5 Old cases of neuritis with unfavourable neuro-electric response: (98% failures) are to be excluded.

XI 131

Sensory changes and the histopathology of nerve fibres before and during the treatment of leprosy

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Skin biopsies were taken from lesions in untreated patients suffering from all forms of leprosy. Before each biopsy, the patient's overall nerve damage was assessed clinically, and this was followed by detailed sensory testing of the area to be biopsied, using graded nylon bristles. In addition, small biopsies from the radial nerve at the wrist were taken at the time of the first biopsy for comparison with the cutaneous nerves in the skin.

Further skin biopsies were taken from adjacent sites after six to twelve months' treatment, and in a few patients the nerve biopsy was repeated.

An account will be given of the neurohistological appearances and of the clinical findings before treatment, and their significance will be discussed.

XI 132

The electron microscope study of the mechanism of nerve involvement in leprosy

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By the electron microscopy of the biopsied peripheral nerves taken from various types of leprosy cases in our laboratory during these 10 years, it was found that the Schwann cell of the cord of Büngner is a special area of the nerve tissue where there is no effective defence mechanism against leprosy bacilli. Because of this, bacilli can remain for a long period in Schwann cells even in the tuberculoid type of leprosy. The endoneurial tissue outside the Schwann cell, on the other hand, shows the same tissue reactivity as that of the skin.

As to the rôle of the axon in leprosy infection, bacilli can be encountered sometimes right in the axoplasm. It seems possible that the naked axon in the extreme periphery of the nerve might ingest leprosy bacilli directly, although conclusive pictures have not so far been obtained.

These features of human leprosy nerve lesions will also be compared to those of the experimental nerve lesions caused by the intraneural inoculation of leprosy bacilli in experimental animals.

XI 133

Patterns of neurological involvement in relation to chronic and/or recurrent erythema nodosum leprosum

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Thirty-three patients with chronic or recurrent erythema nodosum leprosum were followed up for periods ranging from 1 year to 3 years. Careful periodic assessment of peripheral nerve functions was made, using sensory tests, manual muscle tests and strength-duration curves.

Results

1. There was a significant deterioration of neurological functions – motor and sensory – in relation to ulnar, median and lateral popliteal nerves in the "reaction" group compared with control group of patients with lepromatous leprosy who did not develop "reaction" during corresponding period of follow up.

2. Radial and facial nerves appeared unaffected both in the "reaction" and control group.

3. There was an impressive sex difference in the pattern of progression of neurological deficit.

Conclusions

1. Erythema nodosum leprosum when not adequately controlled appears to result in progressive impairment of neurological function.

2. Sex of the patient appears to be one of the possible determinant factors.

The possible mechanism of production of neurological deficit is discussed.

XI 134

Motor conduction velocity test of the ulnar nerve in leprosy reaction under thalidomide therapy

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Six patients suffering from acute ulnar neuritis as a result of leprosy reaction received thalidomide therapy. Motor conduction velocity tests (CVT) were repeatedly carried out, before and during the treatment. The examinations were performed in a room with partial environmental control. Each point was stimulated at least 20 times and the results were averaged with the help of a digital computer provided with an analogue-to digital converter. The delay, velocity and shape and duration of the evoked response were studied.

In all the six patients, the results showed a marked delay of stimulus transmission during the acute leprosy reaction, as compared with the condition of the nerve before, indicating further deterioration. According to the CVT, there was a remarkable amelioration within a few days after initiation of thalidomide treatment, with eventual return of the CVT values to those before the leprosy reaction. The clinical condition of the nerve followed the CVT improvement within a variable period of time.

XI 135

Patterns of sensory loss in leprosy

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Though leprosy affects many tissues, the major areas involved are the skin, nerves, anterior third of the eyes, testes and the mucous membranes of the upper respiratory tract. These predilections are believed to occur because *M. leprae* finds the cooler areas of the body most favourable for proliferation. The distribution of the nerve trunk lesions and the deficits consequent thereto have been well described; the segments of the trunks involved are in places where the nerves are most superficial and presumably coolest.

The most diffuse loss of perception seen in lepromatous leprosy often does not follow the pattern of specific peripheral nerve deficits nor does it follow the pattern of the diffuse distal symmetrical loss seen in the usual toxic-metabolic neuropathies. Before the stage of complete insensitivity in the upper extremities, there is an apparent sparing of the palms, the antecubital fossae and to a lesser degree the volar surface of the forearms. Several such patients were studied by means of the Barnes Thermograph to establish the temperature patterns of the upper extremities. Areas within the same peripheral nerve distribution, but showing a consistent variation in temperature, were then selected for pain threshold measurements which were carried out by means of a Hardy-Wolff-Goodell Dolorimeter. The most increased thresholds occurred in the cooler areas, whereas lower thresholds occurred in the relative warmer areas.

It is suggested that in moderately advanced lepromatous leprosy the destruction of the fine cutaneous nerve endings occurs earliest in the relative cooler areas of the skin leading to a pattern of sensory loss unique to this disease.

XI 136

Treatment of leprotic neuralgia

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In leprosy, treatment of neuralgia is one of the most important and difficult problems from the viewpoint of prevention of deformity or functional disturbances.

First, many kinds of non-leprotic neuralgias must be excluded from the neuralgias of the leprosy patient. But after that, there remain some atypical leprotic neuralgias such as:

1. The neuralgia that is seen in the progressive stages of leprosy.

1.1 Neuralgia in the active stage of lepromatous leprosy.

1.2 Neuralgia in the active stage of non-lepromatous leprosy.

2. Neuralgia due to allergic leprotic vasculitis.

3. Neuralgia due to scars occurring as the result of 1. or 2. above.

The treatment of these atypical leprotic neuralgias varies from one to the other. It is therefore necessary to detect the characteristic symptoms of each kind of leprotic neuralgia and to differentiate them clinically and pathologically, since the treatment of each one will depend on the precise diagnosis.

XI 137

Leprous myositis – a histopathological study

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It has been demonstrated by Rees and Weddell that *M. leprae* grows by preference in the striated muscle fibres of the footpads of mice.

In this paper a detailed histopathological description of 8 muscle biopsies from leprosy patients is given. Of these 6 are from the striated muscles and 2 from smooth muscles of the dartos tunica.

The lepromatous granuloma infiltrates the perimysium along blood vessels and then spreads to the endomysium. The muscle fibres are seen to contain clumps of bacilli which are possibly carried into them through the blood vessels. Evidently in the smooth muscle fibres of the scrotum bacilli multiply freely to form numerous globi.

M. leprae are present inside striated muscles, and more abundantly in the smooth muscle fibres of the scrotum. The striated and smooth

muscles infected by the organism are subcutaneously placed – an important finding that differentiates these muscles from others. Electronmicroscopic studies were done to confirm the histopathological findings.

The discovery of abundant growth of *M. leprae* inside smooth muscle cells in the skin and the scrotum suggests that Schwann cells are not necessarily the preferential site for growth of *M. leprae* in human body.

XI 138

Perforating plantar ulcer in a child, not due to leprosy

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The author records the case of a patient with spina bifida and spinal cord damage, characterised by bilateral perforating ulcer of the foot. He has not seen the condition described in the literature.

This presenting sign has to be differentiated from leprosy, although plantar ulceration due to leprosy is rare in children. If the patient had other lesions, such as pale hyperkeratotic patches, he suggests that a diagnosis consistent with the pathological findings would be an epidermal naevus.

The author considers that supplementary examinations, especially X-ray, are of great importance.

This thesis is documented with photographs, micro-photographs and histological preparations showing the histological aspects of the condition.

XI 139

Neuritis of the peripheral branches in leprosy

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The neuritis of the peripheral branches is studied in different ways of leprosy, investigating three problems:

1. The importance of the neuritis in the differential diagnosis of tuberculoid leprosy, with other affections that may be confused clinically and histologically with leprosy.

2. The neural alterations of the peripheral branches in the lepromatous and tuberculoid forms.

3. Atypical neuritis, and the study of the evolution of neuritis in the different forms of leprosy.

A comparative study was made of 50 cases of tuberculoid leprosy, and in 57 patients in whom the neuritis was due to other causes; the following conclusions were reached: the neuritis of the peripheral branches in tuberculoid leprosy is constant in 84%, and generally allows the diagnosis to be made from other granulomata.

In the second investigation, 6 tuberculoid and 6 lepromatosous biopsies were examined, with the following results:

(a) The attack on the nerves is constant in both kinds of leprosy, being less in lepromatous;

(b) The perineurium is destroyed precociously in tuberculoid leprosy, but not in lepromatous.

In the third investigation, the neuritis of 17 biopsies of lesions of clinically indeterminate leprosy showed that in 5 histologically tuberculoid structure was present; in 2, lepromatous structure, and in the remaining 10, non-specific infiltration.

In the cases of lymphocytic infiltration only, it was found that those that showed neural destruction (principally of the perineurium) progressed to tuberculoid and the ones with no neural destruction progressed to lepromatous leprosy.

It is thus possible on these findings to predict the evolution of the indeterminate form of leprosy.

XI 139A

Early neurolysis for the prevention of paralysis in leprosy

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We review the cases of neurolysis performed at the Instituto Leprológico Nacional de Trillo from 1954 to the present, a total of 30 cases, of which 27 involved the ulnar nerve and 3 the median.

In 12 cases, we performed peri- and endoneurolysis with simple transposition to the anterior aspect of the elbow.

In the remaining 15, we limited ourselves to a perineurolysis, embedding the freed nerve into muscle tissue with good vascular supply; this involved the epitrochlear muscles at the level of the forearm and the anterior and posterior muscles of the arm.

For the lesions of the median nerve, the carpal tunnel was laid open and perineurolysis then performed.

In 28 patients, the pain disappeared completely, paralysis was stabilised, or did not appear – if the operation had been performed early enough.

There were two recurrences, which were treated by a second operation in one case and by sympathectomy of the second and third thoracic ganglia in the second, both with good results.

Conclusion

We advocate neurolysis with transposition as a preventive measure for distal paralysis.

XI 139B

Nerve condition velocity studies in leprosy patients

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Abstract not received.

REACTIONS – IMMUNOLOGICAL ASPECTS

XII 140

Reaction in leprosy

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The reactions associated with leprosy will be briefly reviewed from the point of view of their recognition, the circumstances of their occurrence, their histological nature and their immunological outcome. They will be dealt with under the following headings:

1. *Downgrading reactions* – associated with a loss of immunity; occur in the lesions of untreated tuberculoid and borderline patients.
2. *Reversal reactions* – associated with an upgrading of immunity; occur in the lesions of borderline or borderline-lepromatous patients during treatment. An analogous reaction may occur in a mild form in the lesions of lepromatous patients on treatment, but without any effective upgrading of immunity.
3. *Exacerbation nodules* – occur in untreated lepromatous patients or during a relapse; they are probably related to histoid nodules. Bacilli are exceptionally numerous.
4. *ENL* – occurs typically at the site of small clinically inapparent skin lesions in lepromatous or near-lepromatous patients. But severe reactions may involve the larger, clinically apparent lesions, in which case necrosis and ulceration usually follow. Polymorph infiltration in the early stage is an invariable feature. ENL is associated with a potentially severe systemic upset and the involvement of reticulo-endothelial or other organs or tissues.

XII 141

The immunological basis of reactions in leprosy

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Two forms of the adaptive immune response can be distinguished both morphologically and functionally. These are the production of circulating antibody by plasma cells in the medulla of lymph nodes and similar areas in other lymphoid tissues, and the cell-mediated immune response (CMI) associated with the proliferation of lymphocytes in the paracortical or thymus dependent areas of lymphoid tissue. Defence mechanisms against mycobacteria are associated with CMI. Mycobacteria cannot be eliminated by humoral antibody alone. In lepromatous leprosy, CMI is so impaired that the body cannot eliminate mycobacteria. This process is reflected by an absence of lymphocytes from the paracortical areas of lymphoid tissue. There is not only impairment of specific CMI for *M. leprae*, but other aspects of CMI have been found to be impaired non-specifically; these include sensitivity to contact with simple chemical agents, and delayed hypersensitivity to fungal and monilial antigens. However, there is no impairment of humoral antibody production, lymph nodes are packed with plasma cells and the levels of circulating immunoglobulins increased. Under these conditions patients develop hypersensitivity phenomena with polymorphonuclear leucocyte infiltration in the skin, resembling the Arthus reaction, and pyrexial illnesses with joint involvement, resembling serum sickness. It is suggested that these reactions are due to reaction between mycobacterial antigens and circulating antibody with the fixation of complement. Other erythematous reactions, in which the cellular infiltrate is mainly lymphocytic, could be due to a partial return of CMI, in which specifically sensitized lymphocytes begin again to react with the mycobacteria.

XII 142

The serological pattern of lepra reaction

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Extensive serological investigations were performed in patients with the various kinds of lepra reaction and, by comparison, in a large

group of patients with lepromatous or tuberculoid leprosy without reaction.

This study was carried out in order to detect a possible serological pattern peculiar to lepra reaction.

In all cases tests for antigammaglobulin and antinuclear factors and thyroglobulin antibodies were carried out. Moreover, the serum protein pattern was investigated by agar-electrophoresis and immuno-electrophoresis, and the serum immunoglobulin levels were estimated. In some cases these immunological aspects were studied comparatively during and after the reactional phase. Finally, the sera were examined for the possible occurrence of free short chains and of low molecular weight IgM-immunoglobulins.

The significance of the results is discussed and the broad overlap of serological aspects between leprosy and lupus erythematosus is emphasized.

XII 143

Histochemical study of ENL lesions and their immunologic significance

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Various histochemical examinations were performed on biopsy material taken from 14 lepromatous patients with ENL lesions at Eversley Childs Sanatorium. The significant findings are:

1. Presence of diastase-resistant, PAS positive, materials in histiocytes as well as bacilli; presence of diastase-labile PAS positive materials in areas of acute inflammation.

2. Presence of colloidal iron positive, hyaluronidase-resistant material in non-reactive areas of lepromatous cell infiltrate; reaction diminished or absent in central portion of micro-abscesses.

3. Presence of Alcian-blue positive material (pH 2·4) in non-reactive areas; reaction less or absent in zones of reaction.

4. Diminution to complete absence of elastic and reticulum fibres in areas of micro-abscesses.

5. Presence of neutral fat and phospholipid in non-reactive areas of lepromatous cell infiltrate; less or no reaction in areas of acute inflammation.

6. Alkaline phosphatase present in blood vessels and in reactional areas where reaction is diffuse.

7. Presence of acid phosphatase and aryl sulfatase in lepra cells of non-reactive zones, reaction is marked and conglomerate; reaction is less, diffuse and particulate in acute reactional areas.

The significance of the foregoing observations, particularly the hydrolytic enzymes and the rôle they play in the pathogenesis of ENL, is discussed.

XII 144

An experimental model in mice for studying the reversal reaction

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It has been assumed that the reactional episodes in leprosy have an immunological basis. However, until recently no model infections suitable for immunological study have been available. Now, for the first time, it is possible to produce a progressive and lepromatous-like infection in mice by reducing their immunological capacity by prior thymectomy plus irradiation (900 r). When such mice are inoculated with *M. leprae* into the foot pads and ears they develop lepromatous leprosy at the local sites with nodular swelling of the foot pads. Animals with this fully developed infection, which at the time had little or no immunity, were made immunologically competent again by the inoculation of syngeneic lymphoid cells from normal mice. The result was dramatic; the nodular swellings of the foot pads became inflamed by the 10th day, but later subsided, at which time the ears showed peripheral absorption. The bacilli rapidly became degenerate and by 5 months the histological picture resembled that of borderline leprosy, with nerve damage. We suggest that the

"reaction" produced by these procedures in mice is comparable with the reversal reaction in man. The evidence for this, together with the immunological changes seen in man following reversal reactions will be discussed.

XII 145

Liver biopsy findings and hepatic antigen and anti-liver antibody in the blood of patients with leprosy

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In 20 patients with leprosy (2 of T type, 16 of L type, and 2 of L type in the reactive stage), histologic examination with liver biopsy was performed. In about half cases of L type, varying degrees of non-specific interstitial hepatitis was seen. In some cases of L type, a precipitation line was found in the beta globulin area by immuno-electrophoresis using the normal serum, the patient's serum, the patient's liver homogenate and the anti-normal-liver homogenate rabbit serum. This precipitation line was regarded as liver antigen in the patient's serum. Our results suggest a direct relationship between development of the clinical picture and liver damage in leprosy.

XII 146

Histochemical reactivity of nucleohistones in leprosy

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We found that lepra cells have a weaker reactivity to alkaline-fast Green than cells in tuberculoid leprosy. The question may be asked, whether the decrease of nuclear staining was due to a competitive blocking by the antigen (in this case, from *M. leprae*), or whether the lack of detectable histochemical material was due to a loss of histones from the cells by their metabolic disturbance. If the first statement is correct, one may explain why, in lepromatous type of leprosy, we find high titres for circu lating antibodies and, on the contrary, in the tuberculoid type of leprosy, the immunological spectrum fails to show the same high titres for circulating antibodies. We feel that in lepromatous leprosy the nuclear histones, being partially blocked by antigens, allow a progressive increase in ribonucleic acid synthesis, and the continuously acting effect of the antigenic stimulus provides conditions for the production of newly synthesized specific proteins, which can be related to the general mechanism of antibody reaction.

XII 147

Variations in urinary aminoacids among patients with leprosy

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In our histochemical study of patients with leprosy, bidimensional paper chromatography showed remarkable variations in the urinary aminoacids, and particularly the presence of alanine and glutamic acid.

Having correlated this finding with the clinical, bacteriological, immunological and anatomopathological development, we found that an increase in aminoacids is present clinically and histopathologically in the regressive cases. No correlation was found with the clinical forms, bacteriology and immunology. A correlation with treatment exists, although no conclusions were obtained.

This study led to the following questions:

In which part of the patient's intermediate metabolism could this variation in the concentration of glutamic acid originate?

How significant is the increase or reduction of urinary glutamic acid in relation to the prognosis and the drug activity?

Only a study which includes a quantitative evaluation of the plasma and urinary acids, together with an analysis of enzymatic behaviour, could offer the necessary basis for an explanation of the metabolic origin and relationship of the variations in glutamic acid and alanine.

XII 148

Some immuno-hematological studies in a group of patients with leprosy

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In a group of 50 patients with leprosy of various clinical pictures and evolution, the following examinations have been carried out:

1. Serum complement activity.
2. Levels of antibodies against pyogenic factors and other microbial antigens.
3. Antinuclear and antigammaglobulin factors.
4. The immunoelectrophoresis picture.
5. The behaviour of circulating eosinophils, basophils and PAS-positive lymphocytes.

The decrease of complement activity observed in some cases, and the other results, are discussed.

XII 149

Study of the thyroid function with I^{131} in patients with lepromatous leprosy

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This study was performed in a group of 80 leprosy patients which included several different clinical forms of leprosy. As regards treatment, the patients fell into 3 groups: those under treatment, those in whom treatment was temporarily suspended, and those who had never had treatment.

All the patients were submitted to the following tests: radioisotope uptake of 2–24 hss.; neck-thigh ratio; thyroxine binding index; and protein-bound radioiodine (PB I^{131} levels in plasma).

Our studies showed these results:

1. Leprosy patients had low uptakes (86·7%), together with a decrease in the speed of thyroid clearance in 79·2%. The other members of the group showed values close to the lower limit of normal.

2. The same tests, repeated after exogenous *TSH* (thyroid stimulating hormone) stimulation of the thyroid in the patients who had never had treatment, disclosed that *TSH* elicited an increase of the uptake, neck/thigh ratios and serum PB I^{131} levels. Those results were considered to be consistent with an existing deficit of endogenous *TSH* in leprosy patients, leading to a secondary low uptake.

3. The TBI and PB I^{131} tests were not sufficient for an appraisal of the blood hormone phase.

XII 150

Graphic bacilloscopy

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In 1954 we published a plan, called the Sommer plan, designed to facilitate the reading of bacilloscopies; this method, which possesses the advantage of graphic interpretation, allows rapid reading of the bacilloscopy and further makes it possible to follow the patient's bacilloscopic course.

It is not at variance with Ridley's Bacterioscopic Index or the Granularity Index, both of which it includes.

The Sommer plan consists of a table in which the abscissa stand for the morphological variations of the *M. leprae* and the ordinates for the number of bacteria:

+++	innumerable bacilli per microscopic field
++	10 to 30 bacilli per field
+	3 to 9 bacilli per field
$+^1$	1 to 2 bacilli per field; few
$+_1$	1 bacillus every few fields: very few.

The squared paper is marked R for red, C for cyanophilous, P for pale and I for colourless for the corresponding staining qualities. Negative reactions are shown outside the square.

We believe that the Sommer plan should be adopted as being the most practical for the interpretation of bacilloscopies.

Bacilli	+++	++	+	$+^1$	$+_1$
Typical					
Isolated					
Granular					
Isolated granules.					

PSYCHOLOGICAL ASPECTS OF LEPROSY

XIII 151

Stigma and the leprosy phenomenon – a sociological perspective

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The presumption of leprosy stigma coupled with the physiological uncertainties of the disease intensifies problems of treatment, rehabilitation and control. An understanding of stigma is, therefore, essential to an understanding of the social epidemiology of the disease.

Current efforts to de-stigmatize leprosy are based on the beliefs about stigma evolved by leprosy workers and patients. A dominant theory holds that contemporary leprosy is stigmatized by erroneous association with Biblical references and that stigma will diminish when social misconceptions about leprosy are corrected. This theory represents a "folk" explanation held by an international community of leprosy workers and patients which, while possessing important adaptive value for patients, nevertheless, is limited as a social scientific explanation of the stigma phenomenon.

The paper attempts an examination of the social historical forces associated with leprosy stigma in the Western world. It seeks to explicate the institutionalization of leprosy as a symbol and the institutionalization of leprosy as a disease, noting that the latter process is not yet complete. The relation of stigma to segregation, and of the latter to theories of etiology, will be examined. Finally, questions will be raised concerning the effect of public education programmes on stigma reduction.

XIII 152

The psycho-social problems of leprosy patients in Greater Bombay

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This report is based upon a study of 3,000 unselected patients attending leprosy centres in Bombay. Enquiry was made concerning the effect of the disease on family and social life, on employment, etc. The following conclusions were reached.

Legislation regarding the employment of leprosy patients in Maharashtra State affects government servants and patients referred by their employers to the clinics. Private patients, and self-employed and unemployed patients do not come within its purview. It was apparent from this that infectious patients, although effectively prevented by the government directive from spreading infection at their work place, were subject to no control on their social movements. Neither the government nor private employers make any provision for those who lose their jobs because of leprosy; they are either ignored, or aggregated by the present legislation.

1. The loss of his job may force a leprosy patient with family responsibility to take to anti-social activities.

2. Unemployment encourages aimless wandering and spreads infection.

The conclusions of the survey are:

1. That the fear of social stigma encourages patients to hide the disease. The need for more vigorous social education about leprosy is emphasized.

2. That physical deformities, especially plantar ulcers, are important correctable factors complicating the rehabilitation problem.

3. That loss of employment is a vital consideration, and discretion and sympathy must be used by the medical officer when judging the need for dismissal, segregation or alternative jobs.

4. For bacteriologically positive patients, a job in a sheltered workshop or a segregated job should be considered, since prolonged unemployment has its own problems.

5. The employment problem is of importance with regard not only to the patient, but also to the economic and emotional stability of the family that may be dependent on him.

XIII 153

The leprosy patient and his illness

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In our scientific concern with leprosy we must not forget the patient as a person, and the profound influence upon him of the imponderable psychological factors that are especially associated with this disease. As a person in society, he is at particular psychological risk. (a) He inherits community ideas that often associate leprosy with isolation and rejection. These may be astonishingly persistent, even in highly sophisticated societies. (b) Community attitudes to facial disfigurement and employment present further problems.

The experience of leprosy is itself depressing, through the effects of impaired sensory perception, muscle weakness, diminished work capacity, and complications and other secondary effects. A vicious circle of psychological trauma is thus initiated, from which few patients are immune.

In dealing with this major aspect of leprosy, we need first to see the patient in the light of his difficulties and offer the considerate approach that accepts him in his abnormality. In leprosy control programmes, the level of care we offer is of the greatest importance. New methods of leprosy prophylaxis are no substitute for the education of the general public, the continuing need of which is stressed.

XIII 154

"Hanseniasis", a substitute for "leprosy"

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"Zaraat" of the Hebrew Bible meant defilement or religious defilement (not hanseniasis) and was recognized on skin, clothes and walls, and led to expulsion from the community, destruction. Its Greek translation "lepra" (scaly condition) had probably the same meaning, hanseniasis being known then as "elephantiasis". Later, "lepra" was extended to many skin conditions, including "elephantiasis". While medical progress identified psoriasis, tinea, etc., hanseniasis remained "lepra" and a "biblical disease", patients being subject to its penalties, and stigmatized by subsequent tales and superstitions. The human, social and medical problems caused by that name, are well known and efforts have been made to change it. An appeal of thousands of patients, defended at the Havana Congress by Perry Burgess, was rejected and educational campaigns to explain and make "leprosy" acceptable were recommended instead. Twenty years elapsed but the pejorative "leprosy" goes on damaging people and prevention, and so it will continue if a medical terminology is not substituted.

The official adoption of "hanseniasis", "mitsudin" and derivatives in the State of São Paulo, Brazil, resulted, in a few months, in the well-being and better co-operation of patients and families and in easier integration with other public health activities. Results of an international inquiry are reported.

XIII 155

Investigation of the psychological world of the Hansen's disease outpatient

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This study is the first phase of an in-depth investigation of the patient suffering from Hansen's Disease who is treated as an outpatient. This project is concerned with the conscious attitudes of the patient: how he views himself and his environment, and how he presents himself to this world. Subjects were thirty-four patients attending an out-patient clinic in Los Angeles, California. A semi-structured interview and an objective personality questionnaire (the Minnesota Multiphasic Personality Inventory) were the procedures employed. The interview covered the following areas: (1) childhood rearing practices; (2) the psychological "climate" of the patient's life at the time of onset of symptoms; (3) the immediate impact of the disease on his initial coping mechanisms, his self-perception, his environmental perception, and his life goals; and (4) the effect of the variable of time on the areas outlined in (3).

Findings included the following: (1) the presence, prior to symptom onset, of a psychologically stressful environment in a significant

number of cases; (2) the degree of secrecy in disclosing the illness to be unrelated to severity of medical entity, demographic, or childhood variables; (3) a significant tendency to view the illness as having profoundly altered the life course; and (4) an almost universal expectation of social rejection should the patient be more self-disclosing regarding the illness than he has been. Correlation of interview and questionnaire material revealed no common "Hansen's Disease personality." There was some suggestion that patients tended to handle emotional problems in either a classically neurotic manner or by means of "somatization" of their problems, depending upon the severity of their medical problem, the "somatizers" being the more severely medically impaired.

XIII 156

The patient-doctor relationship in leprosy

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The general principles of the patient-doctor relationship have been applied to the special case of leprosy. Because of the psychological aspect of leprosy, all knowledge acquired since Freud and up to the present must be taken into account, since psychosomatic medicine has shown that there is a close relation between psychic and physical processes.

In the case of the patient suffering from leprosy, it is not enough to make the physical diagnosis; the whole personal history must be considered, including the psychological state and the personal circumstances, since the patient is interested not only in his cure but also in the relief of his anxiety. Leprosy reactions precipitated by emotional factors provide a clear example of psychosomatic relations in the leprosy patient, and psychological factors may influence the development and course of the disease.

The leprologist should have some knowledge of psychology and be competent to use psychotherapy; the team required to treat a leprosy patient should be directed by such a leprologist, who is ultimately responsible for the patient.

Leprosy is an important public health disease, but health insurance should not hinder the personal patient-doctor relationship; there is a risk that this may be lost as social medicine develops.

The patient-doctor relation has rather special importance in the case of leprosy. The patient has faith in the competence and sense of responsibility of his leprologist. To be effective such a relation demands:

1. Freedom of choice of doctor by patient.
2. Medical secrecy.
3. Freedom of choice of therapy.
4. Direct understanding between patient and doctor.

Since leprosy is an infectious disease – chronic, contagious, crippling and complicated by prejudice – the patient-doctor relation is extremely important.

XIII 157

Social problems of leprosy patients

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Since the problems of leprosy patients differ from the problems of the rest of society, their treatment and solution will also differ. History has not been very helpful in this matter. Though their rights as human beings are not different, they are not given the freedom to exercise them because they are not accepted by society.

Segregation – It is thought that the answer to the problem of leprosy patients is segregation, not realising that this can give rise to so many other acute problems.

Rehabilitation – Then how are they to be rehabilitated? What is meant by rehabilitation? Rehabilitation means to restore a person mentally, physically, economically and socially into society so that he may become independent of outside help. Social, physical, economic and psychological stability are the pillars on which the temple of rehabilitation stands. Among many things that leprosy patients need to understand, the most important is that they must discard their age-old habit of accepting charity and become independent and self-supporting.

At the Marie Adelaide Leprosy Centre, about 400 families have been rehabilitated in this way, and about 500 children are attending schools and colleges.

Those patients who are cured and are not deformed can be rehabilitated. But the possibility of rehabilitating the totally deformed cases (the blind and the mentally deformed) is very slight. This is a great barrier which must be overcome, otherwise other plans and projects may fail.

XIII 158

Family reactions to leprosy in a group of Mexican-American patients

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The purpose of this study was to inquire into the manner in which families of twelve Mexican-American patients with leprosy reacted to the crisis of that illness. Within the Mexican-American culture, families are close-knit and are therefore a significant influence on the individual's behaviour. Thus, understanding the attitudes and perceptions of the family should be important in understanding the patient's own reaction to his illness.

Most of the respondents found it difficult to express their feelings about having leprosy. In an effort to avoid confrontation about the illness, they isolated themselves by limiting their social contacts. A fear of social disapproval of illness among the families was noted. There was doubt, however, that this fear was associated with the illness itself rather than the social attitudes and implications under study to these families. Their fears dealt with what people would say or do to them if they found out that someone in the family had leprosy. Fear of social rejection was found among all the respondents in varying degrees. The main indices used to assess their reaction were in how they felt about telling people about it and what their concerns were regarding the illness.

For many of the respondents, the kind of help they felt was significant at the time of the diagnosis of leprosy was the support and assurance that the family and the doctor provided. Having leprosy could be seen as a definite crisis to the patient and his family.

REACTIONS — CLINICAL ASPECTS AND THERAPY

XIV 159

Lepra reaction

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Lepra reaction appears recently to have come to be identified with "erythema nodosum leprosum" (ENL). This paper brings out some of the more serious of its multi-faceted manifestations, and focuses attention on the far-reaching consequences of some of them. We note that:

1. The incidence and severity of lepra reaction are increasing.

2. Cases of persistent reaction are more frequent.

3. Postulating type of reaction are more frequent.

4. Sudden death sometimes occurs.

We draw attention to manifestations in the skin, bones and joints.

(i) ENL lesions have been encountered in the bulbar conjunctiva, the mucous membrane of the mouth, and urethra.

(a) Subcutaneous nodules (SCN) occurring in large numbers over certain sites (skin and muscles near joints, dorsum of hand, etc.) and subsiding by fibrosis, leave behind plaques of sclerodermic skin.

(b) Pustulating lesions (ENL, SCN) and exacerbated lepromatous lesions. Rarely vesicular eruptions occur, sometimes leading to bullae formation, some of which may become haemorrhagic.

(ii) Bone and joint manifestations: The bone most frequently involved is the tibia (anterior aspect); the process is one of osteoperiostitis. Recurrent attacks lead to a thickening of the cortex, resulting in a condition similar to "sabre tibia".

The joint involvement is one of arthritis manifesting with pain and swelling around small joints (especially of the fingers), and also large joints. The rheumatoid arthritic type of involvement of finger joints, when neglected, results in bizarre non-paralytic deformity of the finger. Following the attack of arthritis, severe demineralisation in the bones of the affected joint may occur.

XIV 160

Clinical aspects in lepromatous and borderline cases

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The exacerbation of chronic leprosy by acute episodes is an event that can occur in any type of leprosy except the indeterminate. The clinical aspect, the aetiological considerations and the treatment are distinct, depending on the immunological response of the organism to the bacillus.

Lepromatous cases – They present two reactional clinical aspects:

1. *Lepromatous exacerbation* – Activation of pre-existing lesions (nodules, infiltrated lesions, erythematous plaques) with the same structure; visceral and general symptoms usually poorly developed; neuritis.

2. *Classical leprous reaction* – Certain authors insist on calling it by the name of its symptoms: erythema nodosum leprosum. Symptoms present only in cases of lepromatous leprosy:

Skin – Erythema nodosum, polymorphous and necrotic. The first type with special characteristics: no nodules, and repeated offshoots. The polymorphous form is constituted by erythematous patches, papules and nodules and the necrotising form, frequent in diffuse cases (Lucio's phenomenon), with erythematous patches, purpuric and with necrosis.

General symptoms – Fever, arthralgias, headaches, nausea, vomiting, general malaise.

Peripheral nerves – Neuritis and its sequelae.

Other organs – Orchitis and epididymitis, iridocyclitis, hepato-and splenomegaly. Marked rise in sedimentation rate. The syndrome may be complete, or partial.

Borderline and dimorphous cases – There is no agreement as to the acute manifestations of this intermediate group; the definition is dependent upon the concept and its interpretation and upon all its clinical manifestations. We ourselves consider it as a transitional phase in the

evolution of a case, even though in a given phase it offers an immunological state. Its manifestations are acute: infiltrated lesions which are more or less restricted, annular, squamous; oedema of hands and feet. There is no erythema nodosum (even though some authors state there is). Less marked general symptoms, few lesions in nerves and in other organs. The sedimentation rate is slightly raised, even though it may on occasion be normal or even low.

In order to have an idea of the reactive manifestations of the dimorphous cases, it is necessary first that we should be agreed as to what constitutes dimorphous leprosy and the basis for this conclusion.

XIV 161

The present status of thalidomide treatment in lepra reaction and leprosy

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Lepra reaction – The effectiveness of thalidomide in lepra reaction, as compared with placebo treatment, was demonstrated in 11 patients. In addition, in a "double-blind" study, 173 episodes of lepra reaction in 59 patients, were treated with thalidomide or placebo. Thalidomide treatment was successful in 91% of treated attacks, placebo in 24%.

Fifteen patients treated with thalidomide have been observed for 3½ years. In 5 the reaction did not recur after stopping treatment. In 10, control was maintained by 25–100 mg. thalidomide daily.

Similar results have been published by 9 authors and communicated by 14 investigators.

Further studies are in progress at 5 leprosy centres, under the auspices of the World Health Organization.

Leprosy – Twenty-four patients received 300–400 mg. thalidomide daily for up to 19 months. There was some improvement of the general condition in 5 patients; no improvement in 8, and worsening of the disease in 11. It was concluded that thalidomide is not effective as an anti-leprosy agent.

In 9 patients in whom sulfone treatment was stopped because it appeared to provoke lepra reactions, the use of thalidomide has permitted the continuation of sulfones in therapeutic doses.

Side-effects of the thalidomide treatment are listed. Thalidomide treatment is contra-indicated in pregnant women.

XIV 161A

Thalidomide in the treatment of lepra reaction

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The authors consider the use of thalidomide by many researchers since the pioneering work of Sheskin. They make some comments and evaluate the results of their work in the Sanatorio Aimoré of the D.P.L. of São Paulo, since 1965. Since that date, 1,686 patients have been admitted to that institution, 1,216 of whom had lepromatous leprosy. Four hundred and twenty-five lepromatous patients (321 men and 104 women) were treated with thalidomide for lepra reaction. In most cases the drug was administered in daily doses of 100 mg. (1 tablet). Exceptionally, 200 and 300 mg. were administered.

The series comprised patients manifesting all the symptoms of acute exacerbation (large numbers of EN nodules, neuritis, arthralgia, fever, adenopathy and hepato-splenomegaly) as well as those who had only one symptom, especially neuritis. Previous results were confirmed, for thalidomide was effective in all cases; the mean time before its effect was seen was 5 days.

The symptoms presented by the patients regressed in the following order: fever – skin manifestations – neuralgia. The latter was sometimes quite pronounced, and doses of 100 and 200 mg. of the drug were necessary to bring it under control. In order to obviate the drawbacks connected with the use of the drug in female patients in the child-bearing years, the authors continued to give contraceptives to these patients, as they had been doing since the beginning of leprosy treatment. No striking side-effects attributable to the drug were seen. Some patients complained of drowsiness, dizziness and constipation. A few showed slight oedema in one leg. In one case there were eruptions in the extremities of the limbs; these were erythematous, papulous, vesicular and bullous lesions which disappeared even though the drug continued to be given. The disappearance of clinical symptoms and the erythrocyte sedimentation rate were used for purposes of

therapeutic control. When, after the disappearance of the symptoms, the ESR remained high, the drug was continued, but when the levels continued high with no tendency to fall, the amount of the drug was gradually reduced to a weekly dose of 100 mg., before being completely withdrawn. The patient was then kept under observation.

The authors are of the opinion that thalidomide is one of the most powerful agents we have at present for the treatment of lepra reaction. They believe that the prescription of contraceptives makes its use safe, bearing in mind its teratogenic effects.

They think that the ESR is useful in following the treatment of these patients, and they advocate the use of thalidomide in place of the corticosteroids in all cases of lepra reaction where the patients can be kept under close observation.

XIV 162

Management of lepra reaction

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After defining the term "lepra reaction" and briefly reviewing the standard methods of controlling it, the author gives an account of the use of B.663 (Geigy), a riminophenazine derivative, in the management of about thirty reacting patients in England. B.663 is a dye which is supplied in capsules of 100 mg. and has the unique property of combining a controlling effect on lepra reaction with a therapeutic effect on the underlying leprosy infection. It is safe to administer, and the only side effect of significance is a red-brown pigmentation of the skin with the later development of a grey-black discoloration of the leprosy lesions. Small doses below 100 mg./day are ineffective in controlling lepra reaction, and it is usually necessary to give 200–400 mg. daily at first, later reducing to 100–200 mg. daily. B.663 is suitable for out-patient management and is of particular value in weaning patients from corticosteroids.

XIV 163

The management of erythema nodosum leprosum with particular reference to continued dapsone therapy

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Because, on first introduction, sulphone drugs had to be tested directly in leprosy patients (transmission of leprosy to animals had not then been achieved), it was customary to reduce the dose or stop drug treatment altogether at the slightest sign of any untoward reaction. Nevertheless, since 1959 it has been the considered policy of the Leprosy Research Unit, Sungei Buloh, to continue dapsone in full dosage in erythema nodosum leprosum (ENL). The maintenance of dapsone treatment has not altered the natural history of ENL; in controlled clinical trials, the rate of clinical, histological, and bacteriological improvement has been the same in lepromatous patients with or without ENL, and the long-term prognosis is good.

This policy has enabled more accurate assessment of new drugs to be made in lepromatous leprosy. The indications for steroid therapy in ENL have been better defined, and the role of thalidomide in ENL has been evaluated.

The incidence of ENL in previously untreated patients given dapsone 50 mg. twice weekly is not found to be less than in those given 300 mg. twice weekly. In established ENL, stopping dapsone and changing to another anti-leprosy drug (e.g. thiambutosine or B.663) has not altered the severity of the reaction.

XIV 164

Comparative therapy in lepra reactions

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During the years 1962–1968, we treated lepra reactions (classified on the basis suggested by the Panel on Lepra Reaction of the 8th International Congress of Leprology in Rio de Janeiro) in lepromatous patients with novocain, antihistaminics, corticosteroids, benzydamine, Plaquenil (hydroxychloroquine sulphate) thalidomide, antimony, griseofulvin and indo-

methacin, giving each of these drugs to groups of 20 patients.

The patients who had more than one lepra reaction were treated each time with a different drug.

The results obtained with corticosteroids and thalidomide were very good; those with antimony and haemotransfusions less satisfactory, and those with the other drugs, useless or poor.

The side effects provoked by thalidomide – especially if we consider the length of treatment – were few, fewer than those produced by corticosteroids.

In progressive lepra reaction, thalidomide was given for long periods, which was not possible before, because of the aggravation of symptoms at the beginning of the treatment when small doses of antileprosy drugs were given.

Thalidomide had a favourable influence on neuritic symptoms, although the action was less rapid than on cutaneous lesions.

Antimony (Glucantime) was well tolerated and proved to be moderately effective in the less serious lepra reactions.

Haemotransfusions were less effective and rapid than thalidomide, and effective in patients previously treated with corticosteroids.

Novocain and all the other above-mentioned drugs presented small or negligible antireactional properties, and some of them provoked mild side effects.

XIV 165

The anti-inflammatory effect of G.30.320 (B.663) in erythema nodosum leprosum

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Drug trials on the anti-inflammatory effect of B.663 have, to date, produced conflicting reports. Eighteen lepromatous patients (10 males) with chronic severe erythema nodosum leprosum (ENL) and all corticosteroid-dependent, were treated with B.663, 100 mg. daily. It was possible in all patients to withdraw the corticosteroids and control any further recurrences of ENL with a temporary individual increase of B.663 alone.

In addition, 6 patients (4 males) with severe chronic ENL but not corticosteroid-dependent, responded equally well to treatment with B.663, the dosage being adjusted to their individual needs.

Side effects were minimal, and the hyperpigmentation that developed was accepted by the patients.

It is considered that this drug represents a real advance in the treatment of ENL in that it controls even severe ENL without the use of corticosteroids; in patients who are corticosteroid-dependent, it permits the complete withdrawal of steroids.

XIV 166

Fibrinolytic phenomenon in erythema nodosum leprosum – with special reference to its pathogenesis and treatment

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Since it has been noted that erythema nodosum leprosum (ENL) may improve when synthetic proteinase inhibitors are given, studies were made on 76 leprosy patients (10 tuberculoid, and 66 lepromatous, among whom 46 had ENL and 20 not). Fibrinolytic activity (FA) of both the blood and the affected tissue was studied, using the following procedures: examination of plasma fibrinogen level, Ratnoff's test, Lewis' test, and fibrin plate methods. Results obtained were: (1) Lepromatous patients with ENL showed in both specimens a highly increased FA immediately after its occurrence, and a decrease with the improvement of the reaction. (2) In lepromatous patients thwiout ENL, there was very little increase in FA in the lepromatous tissue immediately after its occurrence. However, when the reaction was of a slightly infiltrative type, significant increased FA occurred with its improvement. ENL may thus result from decrease in proteinase inhibitors followed by increased proteinase activities in lepromatous tissue. A hypothesis on the pathogenesis of ENL is suggested.

XIV 167

Changes in renal function during reactive phases of lepromatous leprosy

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The presence of oedema and changes in cellular content of urine during reactive phases

of lepromatous leprosy led us to investigate renal functions during these phases.

Twenty-six reactive phases and 14 quiescent phases were observed in 26 consecutive lepromatous patients. Daily records of urinalysis and clinical status were made together with weekly records of renal functions.

Results

Significant fluctuations were observed in the red cell, white cell and cast content of urine in the reactive phases compared with the quiescent phases. There was little difference in the respective incidences of proteinuria.

No significant changes were observed in blood urea, serum creatinine or serum sodium, but serum potassium appeared to be lowered in a relatively high proportion of reactive phases.

There was an apparently higher proportion of patients in the "reaction group" who excreted subnormal amount of "water-load" compared with those in the quiescent phase. Inability to concentrate urine was common in both groups.

Creatinine clearance tended to fall in more than 50% of reactive phases. These results are compared with those obtained in healthy staff, patients with uncomplicated lepromatous leprosy with no previous history of "reaction", and other types of leprosy, and those with no history of reaction.

Summary

During reactive phases of lepromatous leprosy, there may be significant changes in the content of urinary deposit, in serum potassium, glomerular filtration and tubular function. In both reactive and quiescent phases of lepromatous leprosy, the functional capacity of the kidney to concentrate urine may be impaired.

XIV 168

Lepra reaction – vascular changes and therapeutics

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The lepra reaction is the general effect of acute and subacute phenomena, cutaneous and general, which, appearing transiently or persistently, modify the chronic course of the disease.

Breakdown of the host-bacillus equilibrium by destruction of organisms by the action of chemotherapeutic agents, liberates bacillary metabolites into the bloodstream and produces a toxi-infective syndrome.

This may be attributed to an enzymatic defect, which may be determined genetically, intensified by the specific action of anti-leprosy drugs and the indiscriminate use of corticosteroids.

Erythema nodosum leprosum (ENL) constitutes the frequent type of reaction in lepromatous leprosy; it is characterised by subacute or chronic nodules, which may relapse or become soft, accompanied by systematic symptoms.

Histologically, extravascular erythrocytes aggregate in inflamed cells; dermal and subdermal vessels, dilated and congested by endothelial swelling, which, thickening the wall, may result in total obstruction; necrotic fat cells occasion the development of lipophagic granulomas.

The Lucio phenomenon is a special type of reaction corresponding to acute vasculitis of the capillaries (and occasionally of the small arterioles), which may produce ischaemic necrosis.

Differential diagnoses may be made between classic ENL, Gougerot-Ruiter syndrome, nodular vasculitis, and Bazin's disease (indurated erythema).

The use of thalidomide (400 mg. daily) permitted the continuation of active specific therapy, accompanied by diminution or suppression of the reactional state.

XIV 169

Epithelioid cell reaction in lepromatous leprosy

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In Japan, since before the chemotherapeutic age, many doctors have seen epithelioid cell reaction in lepromatous leprosy, such as secondary tuberculoid or acute infiltration. After the war, chemotherapeutic drugs are being used in leprosy, and this reaction is increasing, not only in Japan but also in other countries.

Epithelioid cell reaction in lepromatous leprosy may be divided according to its different causes into two groups: primary and secondary.

Genetically, the primary one indicates an essential improvement in the disease, but the secondary one is the exacerbation that occurs in the latent or quiescent stage of leprosy. Nevertheless, these two are clinically, histopathologically and immunobacteriologically the same as tuberculoid leprosy.

The clinical findings of these reactions will be shown, and also the differentiating features.

The relation of this reaction to the problem of classification of leprosy will also be discussed.

XIV 170

Study of reaction in tuberculoid leprosy

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Detailed clinical, bacteriological, immunological and histopathological investigations were made in 46 cases of tuberculoid leprosy showing typical reaction.

The clinical investigation showed that a primary lesion was present in 44 patients in whom new thick erythematous lesions developed suddenly. Intercurrent diseases predisposed to reaction in 80%, and childbirth in 4 out of 6 female patients. In no case could reaction be ascribed to DDS. Reaction was observed in 23 patients during the hot months.

Routine bacteriological examination revealed a slight degree of positivity in 19 patients, and a moderate degree in 2. Two patients in the bacteriologically positive group and one in the bacteriologically negative group had a negative reaction to lepromin, but the rest were positive.

The cells of the epidermis were ballooned in 17, and the basal cell layer was infiltrated in 26. Inter- and extra-cellular oedema was present. Changes were seen in the reticulin, collagen and elastic tissues. Fine lipoid droplets were seen in the epithelioid cells in 4 patients. Mast cells were found degenerated and without granules. Their number was less than in quiescent tuberculoid leprosy. The histamine content of the affected tissue, measured pharmacologically, was less than that of normal tissue or tuberculoid tissue. The patterns of serum protein were investigated. In addition, routine blood, stool and biochemical investigations were made.

XIV 171

The structure and function of the liver in lepromatous leprosy patients and the influence of modern anti-leprosy drugs on them (histochemical and biochemical aspects)

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The results of examination of liver tissue removed by needle biopsy in 53 lepromatous leprosy patients, in combination with the analysis of serum of 88 cases, show that there is an affection of parenchymal elements of the liver with specific alteration of this organ. At the same time as the morphological changes take place, the function of the liver cells is disturbed; there is decrease in ribonucleic acid, in the acido-reduction of ferments and in glycogenesis. Functional tests show impairment of enzyme activity, and disturbance of protein and pigment metabolism.

There is no correlation between the pronounced granulomatous process in the liver and the severity of the disturbances observed in the serum of these patients.

There is a certain parallelism between nonspecific morphological changes, and functional disturbances of the liver. There is a distinct correlation between the results of protein tests and the indices of pigment metabolism on the one hand, and the degree of protein dystrophy and cellular infiltration of portal tracts on the other. Thus the disturbances of liver function noted by many authors is the reflection of nonspecific affection of this organ in leprosy patients.

That the liver parenchyma may be the site of toxic action of anti-leprosy drugs, was confirmed by our observations of patients who had received specific treatment without "protection" of the liver. The treatment of these patients aggravates the disturbances of protein and pigment metabolism that may provoke the development of drug hepatitis. The giving of substances that "protect" the liver simultaneously with the specific therapy, decreases the morphological and functional disturbances, and prevents the development of the complications due to the hepatotoxic action of the drugs. Out of 22 patients treated without

"protection" of the liver, jaundice was noted in 10; while out of 45 treated in whom the liver was protected, only one developed jaundice.

XIV 172

Treatment of leprosy reaction with thalidomide

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The authors treated 25 leprosy patients in reaction with thalidomide in a daily dosage of 100 to 300 mg. All the patients treated (aged between 18 and 68) had erythema nodosum leprosum (ENL) or polymorphous erythema, with pain, with or without raised temperature.

Improvement was observed in all cases, after a varying interval. The first sign to disappear (usually within 24–48 hours) was the raised temperature. The skin condition improved more slowly, beginning some 48 hours after treatment had been begun.

One patient, after 15 months' continuous treatment with thalidomide, had a violent exacerbation of the disease, with ulnar neuralgia, which was controlled by increasing the dose of thalidomide to 500 mg. per day. This may indicate that continuous use of the drug may result in decreased effectiveness.

In some patients it was necessary to interrupt specific leprosy treatment in order to obtain any response to thalidomide.

There was no instance of intolerance to the drug, except for one patient aged 68, who reported some discomfort when the dose was increased from 100 to 200 mg. The only side effect we observed was oedema of the ankle. This, however, was not a reason for stopping treatment.

XIV 173

Treatment of erythema nodosum leprosum with B.663

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Twenty-five patients (23 Bantu and 2 Coloured) were given B.663 for severe erythema nodosum leprosum (ENL), which had previously recurred for periods varying from 2 months to 5½ years (average 2 years). Previous treatment had consisted of 10–40 mgm. prednisone almost daily. B.663 was administered for from 13 to 63 (average 37) weeks. The daily dose, initially 100 mgm., was increased to 300 mgm. in 18 patients and to 400 mgm. in 5. After obvious improvement, the dose was gradually decreased. All patients improved, and in 16 (64%) the results were excellent, i.e. prednisone was no longer needed and ENL was completely or almost completely controlled when the patient was receiving dapsone in standard doses. Prednisone was stopped after an average of 19 weeks. All patients accepted the pigmentation and no side effects necessitating interruption of treatment were encountered. Marked improvement in neuritis was noted in 4 patients in this series, as well as in 5 other patients who were treated with the drug for neuritis alone. An average of 10 weeks was required for maximal improvement. Of 12 patients in whom B.663 was stopped on cessation of symptoms, it had to be given again in 5, an indication that a maintenance dose may be required.

XIV 174

The use of B.663 in the treatment of Chinese leprosy patients with chronic reaction

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Thirty Chinese patients with lepromatous leprosy in chronic reaction have been treated for a period of 12 months with B.663.

The overall results are very encouraging, most patients becoming free from reaction and showing good reduction in bacillary index (BI) during the treatment with B.663. Clinically there was consistent improvement in skin texture and condition, as the erythema nodosum leprosum and oedema subsided. Subjectively, there was marked improvement in the patients' attitude, and even those who did not show great improvement in the rate of skin clearance became more cheerful, more co-operative and more active.

The skin discoloration varied from patient to patient, proportional to the total dose of B.663: it did not constitute a real barrier to the use of the drug amongst patients who had bad

reaction and a slow reduction in BI, but it did deter those who had only mild reaction or a rapid reduction in BI.

The effective weekly dose of B.663 was found to vary between 600 and 900 mgm. for the average patient weighing about 100 lbs. At this dosage, skin discoloration was rarely intense.

No other undesirable side effects were noticed; the drug was well tolerated, even by those with a past history of gastritis or gastric ulcer.

XIV 175

Phenazine derivative (B.663, or G.30.320) in the treatment of lepra reaction

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The author recalls the observation that in patients with lepromatous leprosy seen in collaboration with Vernon Knight in the Public Health Hospital, Bethesda, USA, lepra reaction was controlled with G.30.320.

He refers to our ignorance of the pathogenesis of the lepra reaction, especially its frequency, and the problem that it presents in the regular treatment of patients with lepromatous leprosy with diamino-diphenyl sulphone.

He describes the clinical investigation of the activity of G.30.320 on the lepra reaction, principally in lepromatous patients with the serious and recurrent types. The patients were chosen from the Dermatological Institute of Guadalajara: their clinical history was known; histopathological, bacilloscopic, photographic and other studies were made both before and after the period of the trial.

The author concludes by evaluating the results obtained; he considers that the drug has an important place in the control of lepra reaction.

XIV 176

Corticosteroids in the management of reactional states in leprosy

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Corticosteroids can be safely and effectively used in the resolution of inappropriate tissue responses to the presence of *M. leprae*. This use is of the greatest value in controlling neural involvement, and of lesser, yet significant, importance in the management of other and early complications of leprosy. We have found that if used judiciously, corticosteroids are effective in minimizing all those conditions commonly and collectively called "Lepra Reactions".

In leprosy of any type in which there is peripheral neuritis, steroids can be given in relatively large doses; in almost every instance they cause the infiltration to subside quickly. The threat to the functional integrity of the nerve is averted. The cutaneous reactional states in tuberculoid leprosy are likewise readily controlled.

In complications of lepromatous leprosy, the response is not so dramatic, yet it is still of real value, as it allows the continuation of effective anti-leprosy therapy while subduing *erythema nodosum leprosum*, acute exacerbation, iritis, or any other reactional condition.

This presentation reviews 100 illustrative cases, giving the dosage scheme for corticosteroids, and the appropriate supporting therapy, thus documenting the effective control of those devastating sequelae of an otherwise non-disabling and transient infection.

XIV 177

Hepatic lesions in lepromatous patients

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Review of hepatic lesions in autopsies in the last 10 years. Some are specific (lepromatous hepatitis); others consequential (hepatic fibroses) through disturbance of the reticuloendothelial system in pure lepromatous leprosy (amyloidosis); others are accidental, without relation to leprosy (circulatory stasis, fibrosis, hepatitis, cirrhosis, etc.) or the result of the toxic action of drugs used in treatment.

We studied lepromatous hepatitis and hepatic amyloidosis related to the presence of "lepromas", which are more common and advanced in the liver than in other organs. In patients treated and rendered "negative", these hepatic "lepromas" persist, but are demonstrable only with difficulty by routine techniques.

Amyloidosis of the liver occurs less frequently and later than in the kidney. Histochemical investigation is very complex and differs from case to case.

Authentic "lepromatous cirrhosis" does not appear to exist, except cicatricial fibrosis, which may be so intense as to simulate cirrhosis. These cirrhoses may result from intercurrent viral hepatitis or toxic action. Differential diagnosis of "lepromatous post-hepatitis" from hepatic fibrosis of congestive cardiac insufficiency is difficult histologically.

To reach a diagnosis, renal and hepatic biopsies should be made. Renal biopsy examination provides evidence of amyloidosis, and hepatic biopsy will show lepromatous hepatitis. The existence of liver reservoirs of mycobacteria in apparently cured patients may explain unexpected relapses.

XIV 178

The lupus erythematosus cell phenomenon in reactional phase of leprosy (erythema nodosum leprosum)

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It was Bonomo *et al.* who described for the first time the lupus erythematosus (LE) cell phenomenon in leprosy (4 out of 10 lepromatous (L) cases). The results obtained in the present study were as follows: fifty-two of L cases with (14 males, 4 females) and without erythema nodosum leprosum (ENL) (30 males, 4 females), and 5 of Borderline cases (4 males, 1 female) were examined for LE cell phenomenon. The test was conducted by both *in vivo* (Zimmer-Hargraves' two-hour clot technique) and *in vitro* methods. Out of them, 11 L cases with ENL gave positive results for the test. These were all male patients showing positive C-reactive protein reaction and an increase in IgG. Analysis of LE factor in the ENL sera conducted by gel-filtration with Sephadex G-200 and DEAE Sephadex A-50 (batch method by Baumstart), revealed that the factor was found in 7SγG (S_{20w}= 6·13) in the serum. Perhaps the LE factor in ENL may be somewhat different from that in systematic lupus erythematosus because none of the ENL-sera was positive for the LE test.

XIV 179

Treatment of acute exacerbations in leprosy with indomethacin

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Indomethacin, a non-steroid anti-inflammatory drug, was tried in 31 leprosy patients in acute exacerbation (19 lepromatous, 5 intermediate, and 7 tuberculoid) with predominantly skin manifestations of the type of erythema nodosum leprosum or tuberculoid lesions in reaction, with or without severe neuritis.

The results of the preliminary clinical trial indicate that the drug is an effective analgesic and relieves neuralgia and arthralgia. The skin lesions, however, do not respond favourably, and may at times be aggravated. The drug was well tolerated, and there were very few side effects.

XIV 180

Thalidomide in the treatment of leprous reactions

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We are reporting our results after two years of experience in the treatment of reactions in leprosy. We have treated 88 lepromatous patients, 67 with reaction states of a generalised nature, 15 with severe reactional neuritides, two with iridocyclitis, and two with orchitis and epididymitis. Of the 67 patients with generalised reactions, 46 had only one reactive episode, and 21 had various lesions.

The total number of acute reactional episodes treated with thalidomide was 122. The doses used varied between 100 and 400 mg. initially: 3 had 400 mg., 45 had 300 mg., 57 had 200 mg. and 17 had 100 mg.

In all patients, the reaction disappeared; we studied the effectiveness and the speed of action of the drug on the various reactional syndromes: fever, pain, cutaneous lesions, etc.

Since we began using thalidomide at Fontilles, it has not been necessary to give steroids. There has been a reduction of the number of

patients undergoing reaction; this is attributable to the lower recurrence rate in patients treated with thalidomide.

XIV 181

Renal lesions in leprosy

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We have studied 365 in-patients at the Fontilles leprosarium. The renal function was assessed by means of the clinical history, examination of the blood, urea, renal tests, electrophoresis, etc. We noted that 310 of these patients had some specific renal lesion. In 90% of the cases, the leprosy was lepromatous. Renal lesions account for 80% of the deaths of patients with leprosy.

All the patients had had leprous reactions on repeated occasions during a period ranging from one to five years.

In all cases, the renal lesion appeared in relation to the reactions; it began with proteinuria, which progressed eventually to renal failure. We have studied the time of appearance and the duration of the nephropathy, which shows a progressive course with a fatal issue.

We have analysed the autopsy reports, which reveal nephrosclerosis with amyloid degeneration.

We stress the importance of the reactional states in the pathogenesis of these lesions, which are refractory to treatment and the maior cause of death in leprosy.

THE REHABILITATION OF THE LEPROSY PATIENT

XV 182

Social problems in leprosy in highly endemic countries

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The cherished slogan: "leprosy is a disease like any other disease" is not put into practice – more's the tragedy.

1. Doctors refuse treatment, hospitals refuse to admit leprosy patients. This discrimination against sufferers from disease was omitted in the Declaration of the Rights of Man. There is no legal protection for leprosy patients. There exists an urgent need to improve education in medical schools; most experts are unaware of leprosy; doctors go for postgraduate studies to countries that have no leprosy problem. Education in leprosy is needed at all levels: patients, public, social workers, authorities . . . and political leaders.

2. Medical, social, welfare and charitable activities can find a place at the level of the family by means of mobile units.

This broad public health concept of "leprosy control" is the only total rehabilitation without dislocation and without aftercare relocation problems. The social work is outside, not inside the institutions. Patients must be able to claim temporary admission for special treatment in any hospital. "Homes" are needed only for extreme cases.

3. The delicate *problem of priorities* is one of conscience. Unless resources are immensely increased, all leprosy work remains limited in its goals. Not leprosy, but lack of treatment facilities, has allowed deformities to develop over the last 25 years. The existing social problems are the measurements of our neglect.

XV 183

Social integration the ultimate goal of rehabilitation

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Past hopelessness regarding leprosy rehabilitation is reflected in Mr. Perry Burgess's proposal of "a world within a world" (1946). The author's rebuttal, graciously accepted by Burgess, is: a world within a world is "a world *without* a world".

In the 1950s the author kept on opposing employment in conditions of isolation from the rest of the community. This insistence has paid rich dividends. Instances of integration of leprosy rehabilitation with that of other types of disabled are mentioned. A watching brief for the leprosy patient is, however, very essential in the process of integration.

In the 1960s the author has moved away from his rigid opposition to rehabilitation centres mainly or solely for leprosy patients. He now recognizes that local needs may demand them. Economic rehabilitation promotes social rehabilitation. But he insists that employment alone is not enough. "Full employment in a free society." should be the goal.

XV 184

Leprosy rehabilitation in Japan

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In the past, Japan followed the policy of compulsory segregation of leprosy patients. At present, 93·1 % of the patients are in institutions. Compulsory segregation, however, has recently been abolished and rehabilitation of patients is being encouraged. At Aiseien National Leprosarium, the patients are divided into 3 groups: those who need therapy, the disabled, and a colony consisting of less serious cases. Rehabilitation is dealt with as a problem common to all. The restoration of young patients presents little problem, whereas that of older patients is difficult. Re-admissions to our leprosarium are mostly due to financial reasons and rarely to relapse. In Japan, medical rehabilitation is in sight of attaining its goals.

A difficult problem lies in the fact that many patients are in a state of "institutionalization" (Kamiya *et al.*) and do not possess the will to be rehabilitated. Another difficulty lies in the

lack of a receptive attitude on the part of our society towards the patients, a fact which is based on traditional prejudices. Efforts are being made to correct these prejudices. The rehabilitation of leprosy patients will be brought about only when their mental attitude has been changed by overcoming this institutionalization.

XV 185

Rehabilitation and integration of the leprosy patient in the community

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Inasmuch as the problem of rehabilitation of the leprosy patient who is cured of the disease, is an important and very difficult part of the campaign to combat leprosy, new measures have to be taken to find a solution, since this misfortune has a higher incidence in the underdeveloped countries and countries of poor economy.

In spite of all the advances made in the field of leprology today, the leprosy patient continues to be (in almost all countries) the most feared of all diseased persons. The low regard with which he has always been held persists until today even in the most advanced civilizations. Despite the continuing intensive educational programme by governments and social workers, the patient with leprosy must still keep his sickness an absolute secret, so that he can be reintegrated into society.

There are private agencies working in Brazil to combat this negative attitude. They make valuable and important contributions to those suffering from leprosy, and also run Educandarios, which are foster homes for healthy children, one of whose parents has leprosy. The Educandarios take care of these healthy children while their parents are separated from them. These children provide evidence that there is absolutely no danger of contagion. Here also training is provided for the children in useful elementary skills, enabling them to provide their infirm parents with loving understanding and material help, and looking forward to the re-establishment of a happy home.

More emphasis must be given to psychological preparation in the leprosarium itself. This is the job of the social worker, to prepare the patient who is soon to be released.

Agreements must be made with the Government for the patient who contracts leprosy to receive the same benefits as a worker who is injured on his job. This would be proportioned to the degree of deformity, and should include occupational therapy for the best use of his abilities and to assist him in returning to his rightful place in society.

XV 186

Rôle of the welfare organizations in the medical and social rehabilitation of leprosy patients

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The extent of the leprosy endemic in the world and the high percentage of disabilities caused by this disease, raise problems not only from the epidemiological and medical, but also from the socio-economic and financial points of view.

Because of the important part played by the welfare organisations in the field of rehabilitation, it seemed to us that it would be interesting to show the sums spent by these organizations in favour of disabled or handicapped leprosy patients.

The information received from organizations in many countries is incorporated in this paper.

XV 187

Our experience in the social rehabilitation of leprosy patients

M. GIMÉNEZ

Programme for the Control of Leprosy in le Chaco, Argentina

The author analyses the scientific basis and the social factors of the present complex problem of leprosy. After a brief historic review of achievements in leprosy in the last three decades, based on the experience gained in the Province of Chaco, Argentina, according to the pattern of the leprosy control programme, i.e. dynamic rather than static, he arrives at the following conclusions:

1. There is no rehabilitation of leprosy patients without health education of the population.

2. This education must be based on present knowledge of the disease without hiding any of its aspects.

3. This knowledge will convince healthy people not to fear the disease. This fact facilitates the patient's treatment and his integration in the community.

4. The community must participate actively in this process, and not restrict their interest to providing funds.

5. The basis of the leprosy patient's rehabilitation is the activity of the community and his integration into it.

6. The rehabilitation is the culmination of a slow process, which makes the patient aware of his recuperation.

XV 188

Rehabilitation of leprosy patients

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Rehabilitation remains one of the major problems of the anti-leprosy campaign, even when new and improved schemes of scientific medicine and treatment have been developed. There is no quick and simple answer that will overcome the difficulties of the patient who is ready to return to his home community. The prejudice and ignorance of society still present enormous barriers, which education and information alone will not remove. Some radical change in attitude is essential, and this can only be brought about if all our efforts are directed with a sense of compassion as well as understanding. The early work of Gandhi should serve as a lesson to us all; it was not out of ignorance that his approach to the problems of the leprosy patient was based on an understanding of the various mental and social difficulties as well as on the obvious medical aspects. Early detection, of course, remains the only real answer, but as yet this seems a far-off goal; therefore, we must use the facilities and information that are available to seek the humanitarian and scientific answer to the numerous problems that confront every leprosy patient.

XV 189

Planning of a comprehensive rehabilitation programme in a domiciliary leprosy treatment and control project

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E. S. WILSON S. DORAIPPAN

This paper is based on our experience on a successful trial of a planned comprehensive rehabilitation programme for patients in a domiciliary leprosy treatment and control project in the Gudiyatham Taluk.

The principle of the programme is "preventive rehabilitation" which starts with adequate and skilled patient care in their medical management and in the prevention of avoidable nerve damage. When peripheral nerve dysfunction is already present, prevention of trophic ulceration and loss or shortening of digits and prevention of secondary contractures in paralytic deformities becomes part of the routine work at the peripheral domiciliary treatment clinics. So also are the routine treatment for trophic ulceration and modifications and adaptations of patients' tools.

The base hospital serves for short-term admissions, for reconstructive surgery and for an intensive practical course for vocational retraining for those who need "resettlement". It also serves for neglected cases with severe deformities who need special treatment, surgery or appliances.

This paper outlines the method or organisation and practical effective application of such a programme, as an integral part of a large domiciliary treatment and control programme. Emphasis is laid on minimal requirement of staff and of beds for hospitalisation.

The paper also includes a statistical analysis in some detail of the extent of the problem of disability and the effectiveness of such a programme of preventive rehabilitation in the Gudiyatham Taluk.

XV 190

Rehabilitation services in the prophylaxis and control of leprosy

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Basing his paper on the facts of the prevalence of leprosy in the world as a whole and in the

State of São Paulo, Brazil, the author analyses the public health aspects of the disease and the importance of the physical deformities it causes. He considers that existing statistics reflect a disproportionate number of patients with advanced disease and residual crippling. These patients place a heavy burden on the services of rehabilitation, particularly in the poor, developing countries where leprosy is most prevalent.

There is much to be said for avoiding the expensive reduplication of rehabilitation services necessitated by the provision of special facilities for leprosy patients with deformity, yet on the other hand since leprosy poses many special problems of its own, the author would advocate special clinics, whenever possible, running in conjunction with established rehabilitation centres. These would concentrate on such questions as research into all aspects of deformity in leprosy, the training of technical and auxiliary staff, and the sharing of specialized technical knowledge with the general services of rehabilitation.

XV 191

Epidemiological and administrative views of leprosy rehabilitation

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In the past, surgical and non-surgical restoration and vocational rehabilitation have been greatly emphasized in leprosy rehabilitation. These play a vital rôle in the future life of all disabled leprosy patients, and are within the conventional concept of rehabilitation medicine.

Reports as well as the author's experience indicate that about 30% of leprosy patients have some physical disability. The remaining 70% may become disabled, and may require rehabilitation eventually. Surgical and non-surgical restorative care is costly in manpower and material; therefore, it is economically better to protect the non-disabled 70% from developing disabilities and to integrate leprosy rehabilitation facilities into general rehabilitation services.

The best method for the prevention of disabilities is early case finding, and proper and adequate medical treatment, in conjunction with energetic education of patients. Medical and para-medical workers in leprosy control programmes must be adequately trained in the theory and practice of prevention of disability.

Epidemiological control, medical treatment, prevention of disability, and physical, socio-economic and emotional rehabilitation are integral components of comprehensive health care for leprosy. With these factors in mind, critical reassessment of current programmes is essential to sound planning for the future.

XV 192

The social service as a technical-assistance factor in the prophylaxis of leprosy

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The social problems of leprosy, which are as serious as the medical problems, are analysed in order to determine the necessity for an integrated participation by the social service.

The psycho-economic-social implications, such as the acceptance of the medical diagnosis, and of prolonged treatment, not only on the part of the patient, but also of his relatives; the professional difficulties and their repercussions on the economic situation of the family; the incapacities caused by physical deformities; the problem of the patient's return to his family and his reintegration into society after prolonged segregation, are presented, together with the consequences of the medical treatment. It is necessary not only to be acquainted with them but also to solve them, so that they do not become obstacles to the efficiency of that treatment, and to the eradication and prevention of the disease.

Mention is made of the functions which the social worker, as a member of a team, performs in the dispensary and sanatorium; the development of the work of the social service, through the application of the methods of social case work, social group work and the development and organisation in the community, as well as the use of the patient's potentialities as a human being, the resources of the service for prophylaxis of leprosy and those of the local and regional community.

In conclusion, the results of the social treatment dispensed to cases are discussed.

CHEMOTHERAPY OF LEPROSY—EXPERIMENTAL ASPECTS

XVI 193

Drugs against *M. leprae* in the mouse and in man

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Studies of the anti-*M. leprae* activity of drugs in mice can be carried out by two methods. By the method of continuous drug administration, which has been used in all previous work, the drug is given to the mice continuously from the day of infection to the end of the experiment. By the kinetic method, the drug is administered only for a period of 2–3 months, beginning at a time early in the logarithmic phase; drugs that are merely bacteriostatic allow growth to resume as soon as effective concentrations of drug disappear from the tissues, whereas drugs that are bactericidal prevent growth for a longer period. Using this method, we are studying the activities of a number of drugs. Some drugs previously found active by the method of continuous drug administration have been found inactive by the kenetic method, others merely bacteriostatic, and only a few bactericidal.

To transfer information gained in mice to the treatment of leprosy in man, it is important to have some knowledge of the pharmacokinetics of the drug in the two species. This involves the time course of effective concentrations of the drug and its active metabolites and the relationship to bacterial killing. Fortunately such knowledge can usually be gained. The net result would appear to make it possible to conduct much more meaningful clinical experimentation.

XVI 194

Studies on drug resistance in leprosy using the mouse foot-pad infection

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Hitherto evidence for the emergence of drug resistance in leprosy was entirely clinical. The leprosy infection obtained in the foot pads of mice since 1960 provides a possible method for studying resistance. Once it was shown that multiplication of *M. leprae* from untreated patients was inhibited in this infection when the animals were treated with DDS or other anti-leprosy drugs, it was possible to test whether the multiplication of *M. leprae* from patients relapsing during treatment was similarly inhibited.

The methods used to establish, for the first time, the presence of drug-resistant strains of *M. leprae* in a proportion of patients relapsing during treatment with dapsone (DDS) or with thiambutosine, will be described. Systematic studies have revealed 18 DDS and 5 thiambutosine resistant strains of *M. leprae* from patients in Malaysia, India and Africa. Studies on cross resistance have shown that while DDS-resistant strains are resistant to sulphonamides, they are sensitive to thiambutosine, thiacetazone and B.663, while thiambutosine-resistant strains are resistant to thiacetazone but not to DDS or B.663. Recent studies have revealed strains with intermediate degrees of resistance to DDS, and their relevance for the routine detection of DDS resistance and the emergence of resistant strains in patients on standard treatment, will be duscussed.

XVI 195

An appraisal of the technique for screening antimicrobials against the limited *M. leprae* infection in the mouse foot-pad

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Until recently the testing of potential anti-leprosy drugs was possible only in human patients. Now, the method for transmitting a mild *M. leprae* infection to small rodents (Shepard, 1960) allows this practice to be superseded. Unlike "rat leprosy" (*M. lepraemurium*), which was often used as a model in the past, the experimental *M. leprae* infection reacts successfully to sulphone therapy.

In the present investigation, it is significant that from a wide choice of drugs tested, every anti-leprosy drug (e.g. solapsone, sulphadimethoxine, B.663 phenazine, thiacetazone and thiambutosine), a high proportion of anti-tuberculosis drugs (e.g. INH, PAS, oxydiazolone and viomycin), as well as a few broad-spectrum (e.g. cephaloridine and rifamycin) anti-microbials inhibited multiplication of *M. leprae* in the mouse. Gentamicin was partially effective, oxytetracycline and morphazinamide were ineffective. Also, drugs used for the treatment of "lepra" reaction, cortisone and thalidomide, were without effect. Thus, the procedure is of the utmost value to the screening of anti-microbials in the laboratory. Nonetheless, it is suspected that because of the disparity in the time necessary for treatment and in the mildness of murine infection, the opportunity for evolving resistance is less than in man.

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Experimental and clinical studies on the minimum inhibitory concentration (MIC) of dapsone (DDS) in leprosy

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When the sulphones were first introduced for the treatment of leprosy, the doses used were chosen empirically as at that time no laboratory methods for sensitivity tests were available. Thus, for DDS a dose of 600 mg. weekly became the accepted standard treatment.

Since 1960, when the mouse foot-pad infection with *M. leprae* was discovered, it has been used to determine the MIC of DDS against leprosy in mice. The results showed that mild strains of *M. leprae* from different parts of the world were exquisitely sensitive to DDS, being inhibited by a concentration in the diet that gave serum levels of 0·01–0·02 μg. DDS/ml. It was estimated that such levels would correspond in man to a daily dose of 1 mg. DDS.

The MIC of DDS in mice was accepted as the basis for determining the MIC in man. Therefore a pilot trial was undertaken on 7 previously untreated patients suffering from lepromatous leprosy; they were given 1 mg. DDS daily for 4·5 months. The DDS sensitivity of *M. leprae* from each patient will be determined in mice. Interim clinical and bacteriological results are encouraging, and the results of the completed trial will be presented and discussed at the Congress.

XVI 197

A fluorimetric method for the simultaneous determination of 4,4'-diamino-diphenyl-sulphone (DDS), N-acetyl-DDS (MADDS) and N,N'-diacetyl-DDS (DADDS) in serum or urine

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The demonstration of the inhibition of the growth of *M. leprae* by very low concentrations

of DDS, and recent interest in the possibility of treating leprosy with depot injections of DADDS, have emphasised the importance of devising sensitive and specific methods for the determination of DDS, MADDS and DADDS.

DDS, MADDS and DADDS fluoresce, and there are considerable differences in their fluorescent emission spectra in ethyl acetate. All three compounds are first extracted into ethyl acetate. They are then separated from each other by means of a differential extraction system based on differences in the extent to which each compound partitions between ethyl acetate and dilute hydrochloric acid. The concentration of each compound is then determined from its native fluorescence.

The application of this method to a study of the metabolism of DDS in man is described. After daily oral doses of 50 to 300 mg. DDS, about 20% of the dose is excreted in the urine as unchanged DDS. Much smaller amounts of MADDS and DADDS are excreted in the urine.

XVI 198

Effect of DDS on the growth of *M. lepraemurium* in mouse foot-pads

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The highly suppressive activity of small doses of DDS upon the growth of *M. leprae* in mouse foot-pads has been considered characteristic for both the drug and the infection. This report deals with studies on the effect of DDS in mouse foot-pads infected with another acid-fast organism, *M. lepraemurium*.

Three experiments were performed in mice infected with 5×10^3 *M. lepraemurium* in foot-pads, using 3 concentration levels of DDS, 0·01%, 0·001% and 0·0001% in the diet in each experiment. In addition, a group of animals treated with a very small dose of 0·00001% was included in the last experiment. Growth of bacilli was evaluated by bacterial counts of foot-pads approximately bi-weekly. Definite growth of the organisms was observed at the 12th week after infection. The suppressive effect of DDS was observed on the 18th and 20th weeks in the first experiment, the 18th, 22nd and 24th weeks in the second, and the 20th and 26th weeks in the third. All doses of DDS, including the smallest, showed approximately the same activity with some fluctuation of activity at different time intervals.

Thus, DDS exhibited highly suppressive activity against growth of *M. lepraemurium*, approaching its activity against *M. leprae*, in mouse foot-pads.

XVI 199

Sulfone resistant states

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Diaminodiphenylsulphone (DDS) resistant strains of *M. smegmatis* have been derived in liquid medium to bactericidal concentrations of the drug. The resistant strains were obtained by repetitive transfer. The emergence of resistance was a step-wise process which could only be achieved by exposing the organisms to small consecutive increments in the concentration of DDS.

Exposure of the sensitive parent strain to concentrations of up to 50 micrograms per ml. of DDS resulted in bacteriostasis, even if the exposure period was prolonged for 4 to 6 months. Exposure of the same parent strain to 200 micrograms per ml. of DDS resulted in a complete bactericidal effect. DDS thus exerts either a bacteriostatic or a bactericidal effect depending upon the concentration to which the organism is exposed.

The growth inhibitory effects upon the DDS resistant strains, of a number of anti-leprosy drugs such as diacetyl DDS, B.663, thiocarbanilides and long-acting sulphonamides, together with the emergence of cross-resistance, will be discussed.

The bacteriologic evidence is consistent with the fact that DDS is a structural analogue of para-aminobenzoic acid, and thus its mode of action is that of an anti-folate drug. (Supported by USPHS Grant AI – 08416.)

XVI 200

Biological antioxidant activity of diaminodiphenylsulfonum (DDS, dapsone)

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Diaminophelnysulphonum (DDS, dapsone) added in the ratio of 1:1000 – 1:100,000 to highly pro-oxidant diets, has been shown to have strong biological antioxidant activity. DDS administered to rats on pro-oxidant diets prevents testicular degeneration, the formation of ceroid pigment, and post-mortem renal autolysis. In the presence of very highly pro-oxidant diets, it exerts a biological antioxidant activity superior to that of vitamin E. DDS has a non-specific effect because of its very strong biological antioxidant power, perhaps by stabilising the lipoprotein membrane of the lysosomes.

Anti-leprosy compounds probably owe their therapeutic activity to their biological anti-oxidant power.

XVI 201

Antimycobacterial chemotherapy – microbiological activity of nitro-derivatives and amino-derivatives of dibenzothiophene, diphenylene-sulfoxide and diphenylene-sulfone

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The authors have profited on the one hand by the notion of "closed potential cycles" in pharmacology, and on the other hand by the great therapeutic value of 4,4'-diamino-diphenyl-sulfone since the early work of Fourneau *et al.* (1937) and of Faget *et al.* (Carville, 1941) to the last Symposium on Sulfones, USA-Japan, San Francisco – May, 1967).

They have studied the bacteriostatic and fungistatic activity of 22 mono-nitro and di-nitro, mono-amino and di-amino derivatives of dibenzothiophene, diphenylene-sulfoxide and diphenylene-sulfone.

CHEMOTHERAPY OF LEPROSY— CLINICAL ASPECTS AND THERAPY

XVII 202

B.663 (Geigy) in the treatment of leprosy

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B.663 (Geigy), one of a long series of phenazine compounds synthesized by Barry, is a most potent causal prophylactic in experimental murine tuberculosis. It was first used in treating leprosy patients by Browne in 1960. The preliminary and further reports of the pilot trial suggested that B.663 had a definite action in lepromatous leprosy, causing bacteriological and clinical improvement comparable with that observed with dapsone.

In addition, the non-appearance of acute exacerbation while the patients were under effective treatment with the drug permitted the continuation of treatment in a group of patients who would otherwise have been exposed to episodes of acute exacerbation entailing interruption of anti-leprosy therapy.

Further experience has confirmed the earlier findings, particularly the progressive and rapid fall in the Morphological Index, the concurrent and subsequent fall in the Bacterial Index, the absence of toxicity and undesirable side effects (apart from ruddiness and hyperpigmentation of the skin).

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On the experimental properties of G.30.320 Geigy (B.663)

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G.30.320 is a phenazine derivative with marked activity in lepromatous leprosy. The compound was tested *in vitro* against a wide spectrum of micro-organisms. It particularly inhibits several species of mycobacteria, whereas, with some exceptions, other micro-organisms are not susceptible. G.30.320-resistant strains can be produced *in vitro*. There is no cross-resistance with other tuberculostatic compounds. In experimental infections with mycobacteria (*M. tuberculosis, M. ulcerans, M. johnei, M. lepraemurium, M. leprae*), the compound is active prophylactically and therapeutically at low concentrations. The drug is readily absorbed from the intestinal tract, but very slowly eliminated. It accumulates in the body, especially in fat and in the cells of the reticulo-endothelial system (spleen, liver, lymph nodes). During its stay in the body, the drug is not metabolized to any significant degree. The toxicological findings in animals will be discussed. In standard acute pharmacological tests, G.30.320 is inactive with the exception of an anti-inflammatory and some anti-allergic activity at high dose-levels.

XVII 204

Long-acting sulphonamides in leprosy

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For 20 years DDS has been standard treatment for leprosy. Other drugs have been tried, but generally remain as a second line of treatment. However, recent reports from users of long-acting sulphonamides, particularly the ultra-long-acting Fanasil, suggest the time has come to reconsider the position.

XVII 205

Results of specific treatment of leprosy with long-acting sulphonamides

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Since February, 1958, we have treated 490 cases of leprosy at the Institut Marchoux by

various long-acting sulphonamides administered orally: Sulphamethoxypyridazine (Sultirène); Sulphamethodiazine (Kiron); Sulphadimethoxine (Madribon); Depovernil; Acetylsulphamethoxypyrazine(Acetylazide);Sulforthomidine (Fanasil).

1. We have treated a total of 235 cases of tuberculoid leprosy at the height of their illness, obtaining a 100% cure rate, usually before the second year of treatment, always by the third year.

2. The percentage of lepromatous cases in a controlled trial with disease arrested was as follows after five years of treatment: 89% with Sultirène; 69% with Fanasil; 61% with Acetylazide.

From the practical point of view, we used Sultirène in a dose of 750 mgm. on alternate days for in-patients. For mass treatment we prefer Fanasil 1·50 gm. once a week.

3. All the long-acting sulphonamides were well tolerated, and there were no skin reactions.

The various publications highlight the following points: The undoubted activity of these long-acting sulphonamides in the treatment of leprosy in its various forms. In the lepromatous form, these sulphonamides have an activity at least as high as that of the sulphones, and most authors stress the lower incidence of reaction states of the erythema nodosum type.

Of all the drugs currently in use, the long-acting sulphonamides have the most rapid and the most constant effect on the tuberculoid form.

While the sulphones have either no effect on leprous neuritis or even accelerate the fibrous degeneration, the long-acting sulphonamides have produced good results provided the neuritis is of recent onset.

Finally, Price has obtained good results with Fanasil in 10 patients suffering from a form of lepromatous leprosy resistant to Disulone and to thiambutosine.

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A nine-year trial of sulphonamides in the treatment of leprosy

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On the basis of a prolonged and rigorously controlled trial, the authors conclude that sulphonamides with prolonged action occupy a position of choice as anti-leprotic drugs because of their efficacy, good tolerance and ease of administration.

216 patients were treated: 111 received sulfadimethoxine for periods up to 9 years, 50 sulphormethoxine up to 7, 25 sulphamethoxydiazine up to 3, and 18 sulphamethoxypyridazine up to 2. Twelve patients received an associated treatment.

The best results were obtained with sulphormethoxine as the only drug or associated with enzymes, since for lepromatous patients treated for periods of 2 to 7 years and examined regularly the clinical picture was: cures 20%, distinct improvement 58%, moderate improvement 20%, no change 2%. Nasal mucosa and skin were bacteriologically negative in 84% and 46% respectively. No patients became worse.

No case showed severe intolerance, as shown in skin or blood; the frequency of lepra reaction was 10%.

A comparative study made between the sulphones and sulphormethoxine showed that for the same clinical forms, duration and frequency of treatment, the latter is more active.

Controlled complementary studies should be made to corroborate this impression, which will permit the use of new sulphonamide compounds, a chemical possibility not applicable to the sulphones.

XVII 207

Bacteriological negativity and reactivation of lepromatous patients under sulfone treatment

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This is a retrospective study regarding 807 lepromatous patients registered in the Campinas Dispensary from 1946 to 1968. Classification was based on clinical and bacteriological examinations, lepromin test and, in the majority of cases, on histology. Treatment: DDS 100–200 mg. or Diaminoxil (product similar to Diamidia and Diasone) 1–3 tablets daily, taken for 20 days with 10 days' rest, or sulfones parenterally.

Treatment was considered regular when patients attended the follow-up examinations regularly.

Bacteriological negativity was followed by an observation period of a year, full treatment being continued. The data were computerized; some of the results obtained in ordinary conditions, were as follows:

Accumulated % of bacteriological negativity in patients regularly or irregularly treated

	Regular Treatment			*Irregular Treatment*		
Lepromatous cases	At the end of 3 years	5 years	10 years or more	At the end of 3 years	5 years	10 years or more
L1	79·3%	91·5	97·2	60·0	68·8	84·4
L2	46·1	74·5	94·4	22·4	54·6	82·6
L3	10·4	43·9	86·0	4·5	16·0	62·2

The data indicate that in L1, negativity is achieved in about 80% of cases after 3 years of regular treatment, while in L3 only 10% become negative. Results with irregular treatment are inferior, especially for L2 and L3, and the period required for obtaining negativity is longer.

Accumulated % of reactivation in regularly or irregularly treated patients

	Regular Treatment		*Irregular Treatment*	
Lepromatous cases	At the end of 5 years	10 or more years	At the end of 5 years	10 or more years
L1	7·7%	19·6	10·9	45·0
L2	12·2	27·8	28·1	57·8
L3	14·4	27·8	28·4	62·4

A high proportion of reactivation occurs even after 10 or more years of regular treatment.

These data explain the maintenance of the rate, or the slight and slow decline in the annual rate of newly detected cases. Their importance for control measures is discussed. Other aspects concerning the action of sulfones in conventional and low doses, and the significance of solid-staining *M. leprae* as a measure of the response to chemotherapy are considered.

XVII 208

The management of suspected sulphone resistant leprosy

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Dapsone was first used in Sungei Buloh Leprosarium in 1948–49, but it was not until 1961 that the first cases of possibly sulphone resistant leprosy began to appear. These patients had responded initially to sulphone treatment, but then relapsed and were suffering from active lepromatous leprosy despite apparently regular treatment. Occasional cases have been detected since 1961, and the numbers have increased in the last 2 or 3 years.

We have treated such patients initially with dapsone under rigorously controlled conditions, and assessed their clinical, histological and bacteriological progress. There has almost always been an initial response, but out of 22 patients entered so far in the study, 14 have relapsed after periods of up to 3 years treatment. The mouse foot-pad infection has been used to give objective confirmation that the bacilli were sulphone resistant; and we can now correlate the progress of the patient with his degree of resistance.

The clinical features of patients with suspected sulphone resistance are described together with their characteristic pattern of progress while under treatment with dapsone. If a patient deteriorated, his treatment was changed to another drug, usually the riminophenazine derivative B.663, to which all have responded normally.

XVII 209

Relapse in leprosy in a mass control scheme

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This paper records a study of the relapse rate in leprosy, with reference to:

1. Original type of leprosy, age and sex.
2. Regularity of treatment before inactivity is declared.
3. Regularity in the maintenance treatment period recommended by WHO.
4. Lapse of time between discharge and re-admission because of relapse.

The study is made on about 10.000 patients admitted, examined and discharged in field conditions from 1955 to 1967. The type of disease is determined usually on clinical grounds only, rarely by bacteriological examination, and never by histopathology. About 4% of the patients relapsed with reactivation of former lesions, or presenting a change of type.

While making no claims to precision, the paper investigates the general problem of relapse in leprosy patients in a mass control scheme (about 26,000 registered patients).

XVII 210

The effect of sulfone therapy in achieving bacillary negativity

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The authors investigate the average time necessary for the attainment of permanent bacillary negativity of the nasal mucosa and the skin in lepromatous patients under sulphone treatment, who had been strongly positive before the start of the treatment; and the frequency of bacterial relapse in patients continuing sulphone treatment.

Two groups of patients were chosen:

1. 155 in group A, whose treatment began in 1958, 1959 or 1960.
2. 150 in group B, who had become bacteriologically negative in those years and who continued to receive treatment.

Group A – Number of patients whose nasal mucosa remained bacteriologically positive in 1968: 0.

Average time to achieve negativity: 31 months.

Number of patients whose skin remained bacteriologically positive in 1968: 13 (8·39%).

Average time to achieve negativity of the skin (in the remaining 142): 66 months.

Group B – Bacterial relapse, in the nasal mucosa (rare bacilli): 2; bacterial relapse in the skin (isolated bacilli, or clumps): 30 (20%).

Dosage of sulphone used – In the majority of cases: 100 mg. of oral DDS, daily, or 625 mg. by injection, weekly. In some cases, two tablets of Diasona daily, or 5 ml. of Promin.

The authors comment upon the results obtained and stress the following points:

1. The slow effect of sulphonotherapy on the bacterial picture.
2. The persistence of a not inconsiderable number of patients whose skin remains bacteriologically positive even after about 10 years of treatment (8·38%).
3. An appreciable percentage (20%) of bacterial relapses (in the skin) of patients who continue to take sulphone.

XVII 211

Effect of small doses of DDS in about 9,000 cases of leprosy for over 8 years

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During the last eight years, about 9,000 cases of leprosy (both lepromatous and non-lepromatous) who have been under treatment with small doses of DDS, showed uneventful improvement with scarcely any reaction or sign of intolerance.

The initial daily dose of DDS was 5 to 10 mg. This dose was then very slowly increased (every 3 to 4 months) by 5 to 10 mg. to a maximum of 20 to 25 mg. daily. In exceptional cases, the dose was increased to 50 mg. per day. The improvement of the patients under such treatment has been maintained. Practically no side effects or acute reactions have been seen. The patients became almost symptom-free, particularly those with non-lepromatous leprosy after a reasonable period of treatment.

The salient features observed were:

1. The drug is well tolerated.
2. Few side effects and insignificant reaction noticed during treatment.
3. No development of intolerance; very rare attacks of ENL observed.
4. Practically no sign of drug resistance.

XVII 212

Initial activity, later reduced, of sulfamethoxypyridazine in leprosy

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Sulfamethoxypyridazine has proved in French-speaking countries to be a potent anti-leprosy drug, usually inducing bacillary negativity and clinical healing in the same time as the sulfones. It proved to be one of the less reaction-producing drugs, and seems to be specially useful in the treatment of patients with nerve damage.

It now appears definitely indicated that this drug should not be given continuously for periods exceeding four or five years: after such a period the activity of the drug decreases and clinical relapse may occur. In a few cases, this may be paralleled by a decrease in blood and tissue concentration of the drug. The inefficient absorption may be overcome by parenteral administration. But, in fact, in most cases absorption remains normal, but the disease is not controlled, and hence the sulphones must be given.

XVII 213

B.663 in lepromatous leprosy. Toxicity studies

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Ten patients with active lepromatous leprosy have been followed from 6 to 36 months under treatment with B.663. At intervals of approximately two months, the following laboratory studies were performed: white blood cell count and differential count, platelet count, erythrocyte sedimentation rate, hematocrit, hemoglobin; urinalysis; blood urea nitrogen, fasting blood sugar, cholesterol, total bilirubin, thymol turbidity, total serum protein, albumin, serum alkaline phosphatase, transaminase, creatinine, potassium, calcium, uric acid; stool for occult blood.

Complete general physical examinations, electrocardiograms, X-rays of the hands, feet, and chest, intravenous pyelograms, bromsulphalein determinations, upper gastro-intestinal series; electrical testing of neuro-muscular function; audiograms; and special eye examinations were performed at varying intervals during treatment.

The collected data will be analysed and conclusions presented as to the acute and long-term side effects and toxicity of B.663 in humans.

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Leprosy treatment with a derivative of phenazine B.663 (Geigy)

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Twenty-four leprosy patients were chosen for trial: 21 lepromatous, 2 dimorphous (one in reaction) and one indeterminate. Twelve had received no treatment; 6 had had serious reactional episodes when given various anti-leprosy drugs, and 6 showed little response to the drugs previously given.

The period of treatment with this phenazine derivative varied between 6 and 12 months. The doses were 100 mg. daily, given orally; one patient, with dimorphous leprosy, received 300 mg. daily.

The authors found the clinical and bacteriological results were good (checked with bacterial index and morphological index); the clinical improvement (flattening of the nodules, reduction in infiltration) was obvious after the first few weeks of treatment.

The patients developed pinkish pigmentation of the skin, which was more noticeable in the case of patients with a dark skin than in those with a white skin, especially in the exposed parts.

Laboratory tests revealed no signs of intolerance.

It seemed to us to be a useful drug, comparable with the sulphones, with a speedier clinical effect, during the time and under the conditions of our study.

XVII 215

Clinical evaluation of *Acacia Catechu* (Khadir) in the treatment of lepromatous leprosy

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Studies on the clinical evaluation of medicinal plants for the treatment of leprosy have been in progress for about seven years at the Central Leprosy Training and Research Institute, under the able guidance of Dharmendra and K. Ramanujam. With encouragement and directive from them, controlled trials on herbal drugs were begun at the Research and Post Graduate Institute of Indian Medicine in 1964. A plant, "*Acacia catechu* Willd" (Khadir) of the family *Leguminosae*, which, because of its therapeutic properties, is clearly and emphatically indicated as one of the most efficacious drugs for the treatment of "KUSHTHA" (skin diseases, including leprosy), by various classics of the ancient Indian System of Medicine, was assessed for therapeutic activity in 30 cases with lepromatous leprosy.

In this report, the findings, with reference to clinical, bacteriological and general aspects, are presented. The period of follow-up was one year. Clinically there was significant improvement of the skin lesions in a very high percentage of patients, deterioration occurred in very few, others remained stationary. The bacteriological improvement, although not commensurate with the clinical improvement, was very impressive. Most of the cases improved; marked improvement was seen in the general health as shown by haemoglobin, weight and erythrocyte sedimentation rate of the patients.

On the whole, the results are encouraging and should be confirmed by other research centres.

XVII 216

Madecassol trial in treatment of leprotic trophic ulcers in UAR

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Madecassol is an asiaticoside of the ursane series, and is considered to promote the healing of wounds and ulceration of the leg, stimulating tissue repair.

It was tried on 20 patients in Abu-Zaabal Leprosarium, who had trophic ulcers, some with healthy underlying foot bones and others with necrosed bones. Patients with different types of leprosy, and another 20 cases with similar ulcers, were given the standard treatment for trophic ulcers. All cases were photographed by X-ray and coloured films before and after trial.

One Madecassol ampoule (1 ml. 2%) was given intramuscularly every day, accompanied by Madecassol ointment applied locally in the absence of discharge, or Madecassol powder where there was discharge. The average duration of treatment was 9 weeks. The patient need not be confined to bed to restrict walking.

Madecassol is a very effective drug for promoting the healing of trophic ulcers, especially those not accompanied by necrosed foot bones, and successful results were almost 100%, but in those cases accompanied by necrosed bones healing was less successful.

The presence of necrosed bones leads to prevention or delay of healing of ulceration. The most important advantage of the drug is that it can be used without putting the patient to bed, and he can perform his daily work during the period of treatment, in comparison with the old method of treatment whereby the patient was advised to stay in bed and the results were not so good.

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The therapeutic effect of 4,4'-diacetyldiaminodiphenylsulfone (DADDS) in leprosy

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The respository sulfone DADDS had previously been found effective against *M. leprae*

in mice, and its safety in man had been shown in routine toxicology studies and in trials of its anti-malarial properties. The present report concerns its efficacy in lepromatous leprosy. It was given as an injection of 225 mg. every 77 days to a group of 10 patients, who were matched with a group of 10 patients given oral DDS in a dosage approximating 100 mg. per day. Two chief criteria of therapeutic response were employed, reduction in the ratio of solidly staining *M. leprae* in skin smears and reduction in the number of *M. leprae* in nasal washings. Both criteria are thought to measure reduction in viability of the bacilli, and thus to be appropriate for the measurement of anti-bacterial activity. By both measurements, DADDS was as active as DDS. Two patients receiving DADDS died, but their deaths were not thought to be attributable to drugs. The urinary excretion of sulfones in the DADDS patients also indicated that DDS was being released at a satisfactory rate. (Partially supported by Grant AI 04809 from the National Institute of Allergy and Infectious Diseases, NIH.)

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Some new drugs and methods in the treatment of leprosy

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In the search for rational methods in treatment of leprosy and the prevention of drug-resistance, combined therapy with two or three drugs in optimal doses (taking into account age of the patients and tolerance) has been carried out recently in our Institute. Such treatment was given to 58 patients with lepromatous leprosy who were either untreated (38) or in relapse (20).

The authors consider that sulphones should be used as one of the drugs in combined treatment. It may be prescribed at the same time as thiourea, ethyl mercaptan, or ethionamide. It is advisable to combine oral administration with parenteral and external: e.g. solusulphone + Ciba 1906 + Etisul; solusulphone + ethionamide + Etisul, etc. The combination of drugs should be changed from time to time.

Combined intermittent therapy has made it possible to shorten the length of hospitalization of patients from 5–6 years to 3–3½ in the case of patients taking only one drug. The severity and frequency of acute exacerbations have been reduced.

In some cases the function of the liver improved, coinciding with the clinical improvement in the skin lesions. The cholesterol level was within the normal range, the Van-den-Bergh reaction and bilirubin were within normal limits; the direct reaction (pathological) bilirubin was decreased or disappeared; the aldolase activity was normal; the indices of the sublimate test were increased; the quantity of total serum protein became normal; the albumin fraction increased and the gamma-globulin decreased; the albumin-globulin ratio increased.

It is necessary to investigate systematically the liver and kidney function of all patients receiving intensive anti-leprosy treatment, and, as a prophlactic measure to prescribe lipotropic preparations, amino-acids, vitamins of group B (B_1, B_6, B_{12}) 'insulin, etc., where necessary.

XVII 219

Ethambutol in the treatment of leprosy

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We report the first trial in Mexico of Ethambutol, a drug derived from ethylenediamine and used successfully in tuberculosis, in 20 leprosy patients: 16 lepromatous, 5 of whom showed the lepra reaction, 3 tuberculoid and one dimorphous. The dose was 800 mg. daily, for a maximum period of one year.

From the clinical point of view, 4 cures were obtained, 12 improvements, and 4 were unchanged. The first changes were noted after the first 15 days with 5 patients, and at 30 days with 6: diminished infiltration of plaques, shrinking and softening of nodules (necrosis of the nodules in one patient).

Bacilli became fragmented and granular after the first 15 days, and agglutination of bacilli into a mass was observed in two patients. One patient became bacteriologically negative at two months. There were histopathological changes in every case after the first 4 months,

consistent with reduction in infiltration and bacilli.

We observed no undesirable side effects nor the appearance of lepra reaction in any patient with lepromatous leprosy, but the reaction did not disappear in those patients who had it before treatment.

We gained an initial impression that this drug has an action on leprosy which is more rapid than the usual treatments, but that it appears to produce rapid resistance (appearance of new lesions in the course of treatment) which justifies its combination with other drugs of proved efficacy.

XVII 220

DDS therapy and prophylaxis, and sulfonamide therapy of leprosy – 8 years' observations

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DDS was used in the sanatorium before 1960 in large and irregular doses. There were many serious cases of neuropathic lesions. After 1960, when the dose was reduced to 100 mg. daily for adults, the incidence of such complications decreased, but not to zero. DDS is a good prophylactic for healthy children living with their diseased parents in the sanatorium.

The sulfonamides "Madribon" (sulphadimethoxine) daily, and "Fanasil" and "Kelfizina" (sulphamethoxypyrazine) in a single weekly dose, give good results both clinically and bacteriologically in all types of leprosy – results as good as those with DDS.

These drugs are effective in many cases showing DDS resistance. They also appear to protect against the development of neuropathic lesions, and cure or improve many cases of plantar ulcers that do not respond to DDS therapy.

The author points out that DDS used as a bacteriostatic drug, and the sulfonamides used in neuropathic lesions, and for their protective curing action in DDS resistant cases, have a complementary action in the treatment of different types and forms of leprosy.

XVII 221

Observations on low-dosage sulfone therapy over a 34-month period

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A total of more than 60 patients, all Bantu, who have received DDS in oral dosages ranging from 10 mg. to 50 mg. six times weekly for periods of 6 to 34 months (1965–1968), were studied. Of this group, approximately 40 patients received 10 mg. DDS six times weekly. Patients who were previously untreated, and also those placed on this dosage in an attempt to control reactional states, are included.

Most of the patients had typical or atypical lepromatous leprosy. In addition, observations on several non-lepromatous patients are presented.

A preliminary evaluation of data collected from biopsies, bacteriological studies and clinical progress, suggests that 10 mg. DDS six times weekly is an effective treatment.

The observations reported do not represent a definite study in the nature of a controlled drug trial. Continued observations are planned to determine the long-term results of this treatment, especially with regard to the possible occurrence of relapses, and to introduce additional control measures.

XVII 222

Chemotherapy of leprosy, with special reference to the long-acting sulphones

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There are many kinds of long-acting sulphones. Some show an anti-leprotic action in clinical trials, but others are not only ineffective but may actually appear to make leprosy worse.

In our leprosarium, sulfamethoxypyridazine, sulfadimethoxine, sulfadimethoxypyrimidine, sulfamonomethoxine, sulfasomizole, sulfaphenazole were tried in the treatment of leprosy.

These results will be reported and discussed, and reference will be made to some problems connected with the chemotherapy of leprosy.

XVII 223

Studies on the treatment of leprosy with a synthetic thiocarbanilide, L-4

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A total of 52 leprosy patients (39 lepromatous, 8 tuberculoid, 4 borderline and 1 indeterminate), have been treated with a synthetic thiocarbanilide, L-4. The effectiveness of this drug in the treatment of leprosy is evaluated on the basis of clinical and bacteriological improvement. The results are summarized as follows:

1. L-4, contained in gelatin capsules, can be safely administered orally to the patients after slow induction with initial doses of 50 mg. to 100 mg. daily, and proceeding to the therapeutic maintenance doses of 200 mg. to 300 mg. daily. Only a few patients complained of minor gastric discomfort during prolonged administration of the drug.

2. L-4 has brought significant improvement in clinical symptoms of the patients after a relatively short period, compared with DDS.

3. Changes in granularity indices following L-4 administration were more marked than (or at least equivalent to) those produced by DDS. These changes coincided generally with clinical improvement.

4. Patients with lepromatous leprosy in reaction or those with sulfone allergy responded well to L-4, and showed remarkable clinical improvement. Prolonged administration of L-4 did not provoke reactions in the same way as did DDS.

XVII 224

Treatment of leprosy with a long-acting sulfonamide

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The author presents data on a study with sulformethoxine in the treatment of leprosy, during approximately 24 months. Twenty-five patients were treated (6 lepromatous, 4 borderline and 15 tuberculoid).

He thinks the results were good, especially the attainment of negative bacteriological tests in 4 patients – 3 lepromatous and 1 borderline. He compares the anti-leprotic activity of this compound with that of the sulphones and the thiosemicarbazones, and emphasizes the good tolerance to this drug, and the fact that because of its prolonged action, it is easy to administer (a single weekly dose).

He proposes and recommends the use of the drug as an excellent weapon against leprosy.

XVII 225

Trial of B.663 (Geigy 30.320) in the treatment of leprosy

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Three cases of chronic erythema nodosum leprosum were treated with B.663. During the twelve weeks preceding the preparation of this report, B.663 appeared to control persistent exacerbation in patients who were corticosteroid dependent. A dose of 100 mg. was sufficient in one, while the others required 200 mg. daily. No further episodes of erythema nodosum leprosum have been noted. Clinical and bacteriological improvement has been good. The Morphological Index fell to 0 in four weeks. Leprous ulcers healed rapidly in a severe case. B.663 possibly exerts an anti-inflammatory action, and suppresses acute exacerbation.

Two cases of untreated lepromatous leprosy were included in the study. The average Bacterial Index was 3+. After 8 weeks of treatment with B.663, the Bacterial Index had fallen, and the Morphological Index had fallen to 25 in one and 0 in the other. No signs of erythema nodosum leprosum have appeared, and there has been clinical and bacteriological improvement. Discoloration of the skin was very marked in one patient; the dose was therefore reduced from 300 to 200 mg. per day.

Three patients with painful nerve swellings (one median, and two ulnar) were given B.663 in a dose of 200 mg. daily. No anti-inflammatory agent was administered. During four weeks' treatment with B.663, the signs of acute neuritis had subsided and the nerve swelling had diminished in size.

In all patients, the skin pigmentation was a noticeable side effect. In two cases the skin became icthyotic and crazy-pavement-like. Subjective well-being and marked improvement of the general condition of the patient have been encouraging.

XVII 226

Determination of the minimal effective dose of DDS in leprosy therapy

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It is well known that the patients submitted to sulphontherapy for several weeks show a blood sulphone level of about 0·5 mg.%, which is much lower than the levels attained in the first few days of treatment. A control system is postulated which would maintain the drug at such levels despite some variations in dosage.

Starting from the observation that patients who show improvement in their leprosy lesions have the above-mentioned blood sulphone levels, it is reasonable to suppose that the minimal dosage should be that capable of producing a blood sulphone level of about 0·5 mg.%.

The trial consisted of submitting three groups of patients to three different dosages of DDS: the first one to 100 mg. daily, the second to 100 mg. every other day, and the third to 100 mg. twice a week.

Most patients of the third group may reach a blood level of 0·5 mg.% or so after 3 months' treatment; a dose of 100 mg. DDS daily may thus be too high.

Also, dosages of 300 mg. and even 200 mg. a week, suffice to achieve the same blood level as a dose of 700 mg. weekly.

The blood level is slowly obtained with a weekly dose of 200 mg. or 300 mg. because it takes from 2 to 3 months. It is therefore advisable to start DDS treatment with 100 mg. daily until a blood level of 0·4 mg.% or more is attained, and then to continue with the lower dose.

XVII 227

Findings on the combination morphazinamide-sulphone in the treatment of leprosy

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The author in a previous work presented his findings on the treatment of leprosy by morphazinamide, in which he showed that the treatment was very efficient in advanced lepromatous cases.

Proceeding with his investigations, he has tried to determine the usefulness of the drug in association with sulphone.

In order to do this, he divided a series of lepromatous patients into groups as follows: (a) 17 patients were treated with morphazinamide + sulphone; (b) 19 with sulphone + a placebo; (c) 13 with sulphone without a placebo. Of these patients only 13 in group (a), 15 in group (b), and 8 in group (c) finished the one-year period of observation.

Daily doses of 0·10 g. (1 tablet) of sulphone and 2·0 g. of morphazinamide (4 tablets) were administered.

In order to control the experiment, the following examinations were made: (1) dermatological examinations – at the beginning of the treatment and every month thereafter; (2) colour slides – at the beginning of the treatment, after 6 months and after a year; (3) bacilloscopic indices of the nasal mucosa and of the skin at the beginning of the treatment and every other month thereafter; (4) histopathological examination of skin at the beginning, after 6 months and at the end of the treatment, and finally (5) blood tests (red and white cells), and urine tests.

The evaluation of the results was made after 6 months and after 12 months, as follows:

1. Groups (a), (b) and (c) were compared.
2. After that, groups (a) and (c).
3. And finally, groups (b) and (c).

This was done always having regard to the clinical, bacilloscopic and histopathological changes observed in the patients.

None of the patients showed any side effects that could be attributed to the drugs used. In spite of the well-known harmful effects of sulphone, the patients under observation showed only minor signs of anaemia.

As to reactions of the erythema nodosum and polymorphous erythema types, their incidence was identical in all the groups studied and all were easily controlled with thalidomide.

The author is of the opinion that the combination morphazinamide-sulphone is useful in the treatment of leprosy not only because of its proven efficacity but because it could also provide a way of preventing the development of sulphone resistance.

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Optimal length of treatment for leprosy

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The object of our research is to determine optimal time necessary to cure leprosy in its different forms.

The following are the particulars to be recorded: a meticulous selection of cured patients; a record of different groups of patients in regard to their clinical form and the previous duration of treatment; cessation of sulfone treatment; follow-up of patients over a period of years.

Already, cessation of treatment has raised some difficulties, one of which has led us to the use of a placebo in lieu of DDS.

XVII 229

The effect of rifamycin on leprosy

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For this experiment, 9 previously untreated patients (7 tuberculoid, 2 lepromatous) were selected and hospitalized.

The length of treatment was 8 months; on each of 20 days a month, two intramuscular injections of rifamycin SV 300 mg., were given; 10 rest days monthly. After every two months, clinical and histological tests were repeated. Clinical improvement at the beginning of treatment was rapid, but latterly it became less rapid.

Clinical results

Disappearance of bacilli from the nasal mucosa in under two months.

Regrowth of eyebrows.

No new skin lesions.

Disappearance of congestion of the face.

Rapid healing and cicatrisation of ulcers.

Healing of the perforating ulcers when not complicated by bone lesions.

Improvement in the thick scaling of hands and feet, and the infiltrating lepromatous lesions on the trunk, mouth, penis, scrotum.

Disappearance and repigmentation of well-defined copper coloured macules.

The drug was well tolerated. No adverse reactions developed during treatment, except in one case who recovered within a few days of stopping the treatment; it was then possible to resume therapy.

MISCELLANEOUS

Miscellaneous 230

Is leprosy a stable disease? A historical review

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Since the first description of leprosy in the Mediterranean-European culture about 2,000 years ago, this disease has been described in terms of low resistance leprosy. No recognisable description of high resistance leprosy can be found. Since Danielssen and Boeck (1847), it has been possible to correlate these clinical descriptions with modern terminology. According to Melsom, high resistance leprosy is extremely rare in Scandinavia.

Osteoarchaeological examinations (V. Møller-Christensen) confirm that Danish Mediaeval Leprosy is of the low resistance type.

Literary and osteoarchaeological evidence and modern clinical studies confirm that the individual symptoms of low resistance leprosy have not changed. Minor, relative differences to modern materials may be explained by reference to social and racial conditions (Johns. G. Andersen).

Conclusion

Low resistance leprosy has been stable for more than 2,000 years. This stability may be extrapolated both ways. This is of great interest both to the clinician and the historian.

Miscellaneous 231

Isolation of polysaccharides from *M. leprae* and *M. lepraemurium* and their reaction with sera from patients with leprosy

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The non-availability of pure cultures of *M. leprae* and *M. lepraemurium* has precluded the isolation of immunologically active substance from these organisms. However, this difficulty has been now overcome in part by taking advantage of the identification of the group specific antigen, Polysaccharide I (PolyINb), present in *Nocardia* and *Mycobacteria*. This has been chemically characterized as a polymer of d-arabofuranose and d-galactopyranose in a molar ratio 3:1. Polysaccharides were obtained from lepromatous tissues rich in *M. leprae* after physical removal and enzymatic destruction of all other components that were possibly active immunologically. The method consisted mainly in treating ground tissues, after ultrasonic treatment with deoxyribonuclease, ribonuclease and pepsine, followed by deproteinization by Sevag's procedure. From mice and rat tissues rich in *M. lepraemurium*, pure bacilli were obtained after enzymatic treatment and differential centrifugation. The purified *M. lepraemurium* were subjected to ultrasonic treatment and from the extract polysaccharides were isolated as described above for *M. leprae*. Both preparations of polysaccharides, from *M. leprae* and *M. lepraemurium*, gave precipitin bands in agar plates with some sera from leprosy patients. One of these bands gave identity with PolyINb. Moreover both preparations showed another band of identity between them, which suggest an antigenic relation between *M. leprae* and *M. lepraemurium*. The reaction of crude fractions and the purified polysaccharides with several other sera from leprosy patients is discussed.

Miscellaneous 232

A rehabilitation centre in Iran

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Historical fear of leprosy exists in many parts of the world, especially in Iran. This has been observed even amongst medical people and caused public reluctance to allow the patient to lead a normal life, and encouraged robbery, smuggling narcotics, etc. The mobile unit, dispensary treatment and case-finding are of more theoretical than practical value.

To overcome these difficulties our association (Association d'Assistance aux Lépreux), under the patronage of Her Imperial Majesty the Queen, has established a rehabilitation centre called Behkadeh, for non-contagious patients. The land is a gift of His Imperial Majesty and is more than 25,000 hectares in extent. The administration of Behkadeh is under supervision of the representatives of the Companie Internationale du Développement Rural.

There are 250 inhabitants in Behkadeh, fo whom 112 are ex-patients and the rest are healthy contacts vaccinated with BCG. At an examination last summer, there was no positive case among them.

From among 5,867 known cases of leprosy, plus a yearly increase of 500, those who have reached the stage of non-contagiousness and have 70% ability to work, are sent to Behkadeh and occupied with agriculture, cattle-breeding and handicrafts. Construction consists of public buildings, school, hospital, mosque and guesthouse.

Therefore, Behkadeh is a centre of rehabilitation for people for whom there is no room in society. We hope that we have not created a "damned spot", but a centre of rural development as an example for others.

Miscellaneous 233

Provisional results of the examination of the whole NAESTVED Leprosy-Churchyard, 1260-1540 A.D.

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The excavations I have led during 20 years began in 1948 and will be finished in June, 1968. The material, consisting of the skeletons of more than 500 persons, and representing the inhabitants of the Leprosy Hospital, the sex-ratio, the average age and the survey of the disease, I presented to the Medical Historical Museum of the Copenhagen University in 1959.

At the Congress in Madrid, 1953, I gave an account of the discovery of the facies-leprosa syndrome (FLS). My collaborators and I failed to see then, and during the following 13 years, that the FLS developing during the 5th–10th years of age, obviously causes alterations of the maxillary incisors.

In 1966, my odontological collaborator Knud Danielsen and I unearthed a child's cranium (9 years of age) with FLS. We were astonished to find a marked symmetrical change of the roots of 1+1 of a hitherto unknown pattern. Being convinced that the changes were due to leprosy, we called these overlooked – and probably specific – leprous tooth-changes *dens leprosus*, which now form the subject of Dr. Danielsen's odontological thesis.

Of chronic bone diseases, apart from leprosy, traumatic diseases and arthropathies, we found 2 cases of tuberculosis. There are, however, no cases of syphilis, a circumstance which is of considerable medico-historical importance in the debate concerning the American origin of this latter disease.

Miscellaneous 234

Leprogenic odontodysplasia ("Dens Leprosus")

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According to the literature, maxillary incisors are the teeth most exposed to leprogenic changes.

As "facies leprosa" (rhino-maxillary leprogenic bone changes) may develop early in life, and as maxillary incisor-germs are in close contact with these pathological processes, it is no surprise to find disturbances in the odontogenesis of these teeth in children with low-resistant leprosy.

The typical changes found in my mediaeval material are:

1. One or few concentric constriction grooves (possibly indicating acute exacerbation) round the tooth followed by arrested or abortive root completion, resulting in: from almost total root-absence (main-attack at 5 years) to slight apical deformity (main-attack at 10 years).

2. Irregular pulp-cavity walls.

3. Symmetrical involvement of all 4 upper permanent incisors, possibly with contemporary less pronounced hypolasia in other teeth.

4. Premaxillary growth inhibition with crowding of front teeth, when the main attack occurs before 9 years of age.

5. Only found with facies leprosa (not necessarily conversely).

6. Only found in persons who had died under 20 years of age, indicating a severe type of leprosy.

Similar, but less pronounced, changes are observed in upper and lower canines and premolars; they may be accidental or leprogenic; if the latter, they may – as irreparable processes – be used for later evaluation of attacks in youth.

Miscellaneous 235

An investigation of the factors concerned in the development of intolerance and resistance in patients with lepromatous leprosy under sulfone therapy

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Lepromatous leprosy patients showing intolerance or resistance to sulfone therapy were investigated clinically, bacteriologically, histologically, histochemically, biochemically, immunochemically and electromicroscopically. Of the 83 patients, 11 were untreated, 17 improved, 35 intolerant and 20 resistant.

In intolerant cases large numbers of bacillary fragments can be found in host cells in combination with cytoplasmic proteins, DDS and phospholipids from the bacillary disintegration.

Histology of resistant cases ranged from histoid to fibrolytic patterns. The fulminating type can be seen with innumerable well-stained acid-fast bacilli in almost all cells. The resistance to sulfone therapy may be due to lack of enzymic activity of the host cell cytoplasm to combine with DDS for formation of inhibitory substance to prevent production of essential nutrient for multiplication and growth of bacilli. Therefore the essential nutrient is formed in abundance for the growth and multiplication of the organisms. DDS is eliminated without doing any harm to the bacilli.

In patients who improve, the histology is that of a healed lesion. The epidermis looks normal, and there is practically no cellular infiltration in the dermis. Biochemical reactions suggest the formation of a metabolite with DDS, which acts as an inhibitor of the formation of essential nutrient for the growth and multiplication of organisms. The bacilli disintegrate and are eliminated gradually from the system.

Miscellaneous 236

Existence of a mycolic acid-arabino-galactan-mucopeptide complex in the cell wall of murine leprosy bacillus

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The mycobacterial cell wall contains large amounts of arabinose, galactose and lipids in addition to mucopeptide. Analyses of the residues, after phenol treatment of the cell walls of various mycobacteria, demonstrate that the majority of the cell wall components form a mycolic acid-arabino-galactan-mucopeptide complex.

The chemical composition of the residual substance, after phenol treatment, of murine leprosy bacilli isolated from infected mice is as follows: P, 0·11%; N, 2·65%; arabinose, 15·6%; galactose, 14·1%; amino sugar as glucosamine, 7·6%; amino acid as alanine, 15·0%; mycolic acid, 33·8%. Amino sugars and amino acids are glucosamine, muramic acid, alanine, glutamic acid and α, ε-diaminopimelic acid (1:0·84:2·00:0·97:0·82 in a molar ratio). This composition is similar to that of the phenol-residue of other mycobacterial cell walls, qualitatively and quantitatively.

These data suggest that as far as a mycolic acid-arabino-galactan-mucopeptide complex is concerned, murine leprosy bacillus belongs to genus *Mycobacteriaceae*.